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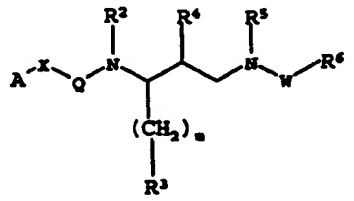

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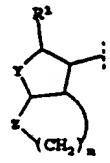

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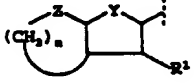

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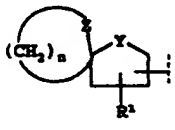

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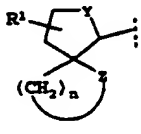

(V)

(57) Abstract

The present invention generally provides a retroviral protease–inhibiting compound represented by formula (I), or a pharmaceutically acceptable salt, a prodrug, or an ester thereof, wherein A is a group of formula (II), (III), (IV), or (V); R^1, R^2, R^3, R^5, or R^6 is H, or an optionally substituted and/or heteroatom–bearing alkyl, alkenyl, alkynyl, or cyclic group; Y and/or Z are CH_2, O, S, SO, SO_2, amino, amides, carbamates, ureas or thiocarbonyl derivatives thereof, optionally substituted with an alkyl, alkenyl, or alkynyl group; n is from 1 to 5; X is a bond, an optionally substituted methylene or ethylene, an amino, O or S; Q is C(O), C(S), or SO_2; m is from 0 to 6; R^4 is OH, =O (keto), NH_2, or alkylamino, including esters, amides, and salts thereof; and W is C(O), C(S), S(O), or SO_2; wherein the compound inhibits a multidrug–resistant retroviral protease. Optionally, R^5 and R^6, together the N–W bond of formula (I), comprise a 12– to 18–membered ring. Also provided are pharmaceutical compositions for, and therapeutic methods of, treating a multidrug–resistant retroviral infection in a mammal.

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MULTIDRUG-RESISTANT RETROVIRAL PROTEASE INHIBITORS AND ASSOCIATED METHODS

STATEMENT AS TO RIGHTS TO INVENTIONS MADE UNDER FEDERALLY SPONSORED RESEARCH AND DEVELOPMENT

This invention was made with Government support under Grant Number GM53386 awarded by the National Institutes of Health. In addition to its existing rights, the United States of America may have additional rights to this invention under the above grant.

TECHNICAL FIELD OF THE INVENTION

The present invention relates to multidrug-resistant retroviral protease inhibitors, compositions, uses thereof, and related methods.

BACKGROUND OF THE INVENTION

Acquired immune deficiency syndrome (AIDS) is a fatal disease, reported cases of which have increased dramatically within the past several years. Estimates of reported cases in the very near future also continue to rise dramatically.

The AIDS virus was first identified in 1983. It has been known by several names and acronyms. It is the third known T-lymphocyte virus (HTLV-III), and it has the capacity to replicate within cells of the immune system, causing profound cell destruction. The AIDS virus is a retrovirus, a virus that uses reverse transcriptase during replication. This particular retrovirus is also known as lymphadenopathy-associated virus (LAV), AIDS-related virus (ARV) and, most recently, as human immunodeficiency virus (HIV). Two distinct families of HIV have been described to

date, namely HIV-1 and HIV-2. The acronym HIV will be used herein to refer to HIV viruses generically.

Specifically, HIV is known to exert a profound cytopathic effect on the CD4+ helper/inducer T-cells, thereby severely compromising the immune system. HIV infection also results in neurological deterioration and, ultimately, in the death of the infected individual.

The field of viral chemotherapeutics has developed in response to the need for agents effective against retroviruses, in particular HIV. For example anti-retroviral agents, such as 3'-azido-2',3'-dideoxythymidine (AZT), 2'3'-dideoxycytidine (ddC), and 2'3'-dideoxyinosine (ddI) are known to inhibit reverse transcriptase. There also exist antiviral agents that inhibit transactivator protein. Nucleoside analogs, such as AZT, are currently available for antiviral therapy. Although very useful, the utility of AZT and related compounds is limited by toxicity and insufficient therapeutic indices for fully adequate therapy.

Retroviral protease inhibitors also have been identified as a class of anti-retroviral agents. Retroviral protease processes polyprotein precursors into viral structural proteins and replicative enzymes. This processing is essential for the assembly and maturation of fully infectious virions. Accordingly, the design of protease inhibitors remains an important therapeutic goal in the treatment of AIDS.

The use of HIV protease inhibitors, in combination with agents that have different antiretroviral mechanisms (e.g., AZT, ddI and ddT), also has been described. For example, synergism against HIV-1 has been observed between

certain C_2 symmetric HIV inhibitors and AZT (Kageyama et al., *Antimicrob. Agents Chemother.*, 36, 926-933 (1992)).

Numerous classes of potent peptidic inhibitors of protease have been designed using the natural cleavage site of the precursor polyproteins as a starting point. These inhibitors typically are peptide substrate analogs in which the scissile P_1-P_1' amide bond has been replaced by a non-hydrolyzable isostere with tetrahedral geometry (Moore et al, *Perspect. Drug Dis. Design*, 1, 85 (1993); Tomasselli et al., *Int. J. Chem. Biotechnology*, 6 (1991); Huff, *J. Med. Chem.*, 34, 2305 (1991); Norbeck et al., *Ann. Reports Med. Chem.*, 26, 141 (1991); and Meek, *J. Enzyme Inhibition*, 6, 65 (1992)). Although these inhibitors are effective in preventing the retroviral protease from functioning, the inhibitors suffer from some distinct disadvantages. Generally, peptidomimetics often make poor drugs, due to their potential adverse pharmacological properties, i.e., poor oral absorption, poor stability and rapid metabolism (Plattner et al. *Drug Discovery Technologies*, Clark et al. eds., Ellish Horwood, Chichester, England (1990)).

The design of the HIV-1 protease inhibitors based on the transition state mimetic concept has led to the generation of a variety of peptide analogs highly active against viral replication *in vitro* (Erickson et al. *Science*, 249, 527-533 (1990); Kramer et al., *Science*, 231, 1580-1584 (1986); McQuade et al., *Science*, 247, 454-456 (1990); Meek et al., *Nature (London)*, 343, 90-92 (1990); and Roberts et al., *Science*, 248, 358-361 (1990)). These active agents contain a non-hydrolyzable, dipeptidic isostere, such as hydroxyethylene (McQuade et al., *supra*; Meek et al., *Nature (London)*, 343, 90-92 (1990); and Vacca et al., *J. Med. Chem.*, 34, 1225-1228 (1991)), or

hydroxyethylamine (Ghosh et al., *Bioorg. Med. Chem. Lett.*, 8, 687-690 (1998); Ghosh et al., *J. Med. Chem.*, 36, 292-295 (1993)); Rich et al., *J. Med. Chem.*, 33, 1285-1288 (1990); and Roberts et al., *Science*, 248, 358-361 (1990); as an active moiety that mimics the putative transition state of the aspartic protease-catalyzed reaction.

Two-fold (C_2) symmetric inhibitors of HIV protease represent another class of potent HIV protease inhibitors, which were created by Erickson et al., on the basis of the three-dimensional symmetry of the enzyme active site (Erickson et al. (1990), *supra*). Typically, however, the usefulness of currently available HIV protease inhibitors in the treatment of AIDS has been limited by relatively short plasma half-life, poor oral bioavailability, and the technical difficulty of scale-up synthesis (Meek et al., (1992), *supra*).

In a continuing effort to address the problem of short plasma half-life and poor bioavailability, new HIV protease inhibitors have been identified. For example, HIV protease inhibitors incorporating the 2,5-diamino-3,4-disubstituted-1,6-diphenylhexane isostere are described in Ghosh et al., *Bioorg. Med. Chem. Lett.*, 8, 687-690 (1998) and U.S. Patent No. 5,728,718 (Randad et al.). HIV protease inhibitors, which incorporate the hydroxyethylamine isostere, are described in U.S. Patent Nos. 5,502,060 (Thompson et al.), 5,703,076 (Talley et al.), and 5,475,027 (Talley et al.).

Recent studies, however, have revealed the emergence of mutant strains of HIV, in which the protease is resistant to the C_2 symmetric inhibitors (Otto et al., *PNAS USA*, 90, 7543 (1993); Ho et al., *J. Virology*, 68, 2016-2020 (1994); and Kaplan et al., *PNAS USA*, 91, 5597-5601 (1994)). In one study, the most abundant mutation found in response

to a C_2 symmetry based inhibitor was Arg to Gln at position 8 (R8Q), which strongly affects the S_3/S_3, subsite of the protease binding domain. In this study, the shortening of the P_3/P_3, residues resulted in inhibitors that were equipotent towards both wild-type and R8Q mutant proteases (Majer et al., 13th *American Peptide Symposium*, Edmonton, Canada (1993)). Inhibitors have been truncated to P_2/P_2, without significant loss of activity (Lyle et al., *J. Med. Chem.*, 34, 1230 (1991); and Bone et al., *J. Am. Chem.* Soc., 113, 9382 (1991)). These results suggest that inhibitors can be truncated and yet maintain the crucial interactions necessary for strong binding. The benefits of such an approach include the elimination of two or more peptide bonds, the reduction of molecular weight, and the diminishment of the potential for recognition by degradative enzymes.

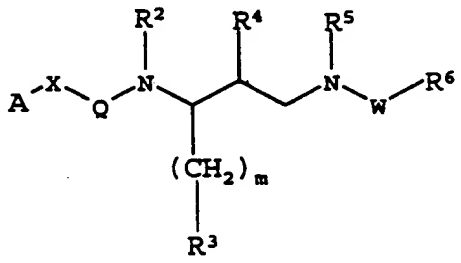
More recently, new mutant strains of HIV have emerged that are resistant to multiple, structurally diverse, experimental and chemotherapeutic retroviral protease inhibitors. Such multidrug-resistant HIV strains are typically found in infected patients, who had undergone treatment with a combination of HIV protease inhibitors or a series of different HIV protease inhibitors. The number of reported cases of patients infected with multidrug-resistant HIV is rising dramatically. Tragically for these patients, the available options for AIDS chemotherapy and/or HIV management is severely limited or is, otherwise, completely nonexistent.

In view of the foregoing problems, there exists a need for inhibitors against multidrug-resistant HIV strains. Further, there exists a need for nonpeptidic inhibitors of multidrug-resistant HIV protease. The present invention

provides such inhibitors of multidrug-resistant HIV protease, compositions, synthesis methods, and uses thereof. These and other advantages of the present invention, as well as additional inventive features, will be apparent from the description of the invention provided herein.

BRIEF SUMMARY OF THE INVENTION

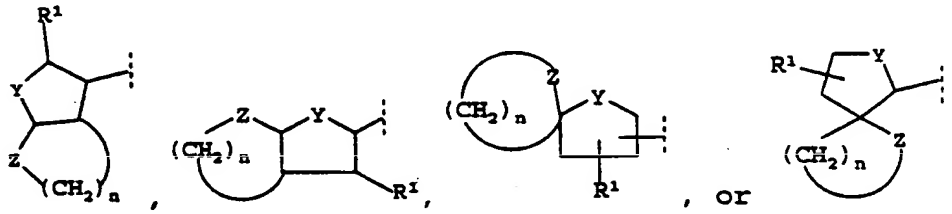
The present invention generally provides a retroviral protease-inhibiting compound represented by the formula:



(I),

or a pharmaceutically acceptable salt, a prodrug, or an ester thereof, wherein:

A is a group of the formula:



;

R^1 is H or an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkylalkyl, an aryl, an aralkyl, a heterocycloalkyl, a heterocycloalkylalkyl, a heteroaryl, or a heteroaralkyl radical, in which at least one hydrogen atom is optionally substituted with a substituent independently selected from the group consisting of OR^7, SR^7, CN, NO_2, N_3, and a halogen, wherein R^7 is H, an alkyl, an alkenyl, or an alkynyl;

Y and Z are the same or different and are independently selected from the group consisting of CH_2, O, S, SO, SO_2, NR^8, $R^8C(O)N$, $R^8C(S)N$, $R^8OC(O)N$, $R^8OC(S)N$, $R^8SC(O)N$, $R^8R^9NC(O)N$, and $R^8R^9NC(S)N$, wherein R^8 and R^9 are independently selected from the group consisting of H, an alkyl, an alkenyl, and an alkynyl;

n is an integer from 1 to 5;

X is a covalent bond, CHR^{10}, $CHR^{10}CH_2$, CH_2CHR^{10}, O, NR^{10}, or S, wherein R^{10} is H, an alkyl, an alkenyl, or an alkynyl;

Q is C(O), C(S), or SO_2;

R^2 is H, an alkyl, an alkenyl, or an alkynyl;

m is an integer from 0 to 6;

R^3 is a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl in which at least one hydrogen atom is optionally substituted with a substituent independently selected from the group consisting of alkyl, $(CH_2)_pR^{11}$, OR^{12}, SR^{12}, CN, N_3, NO_2, $NR^{12}R^{13}$, $C(O)R^{12}$, $C(S)R^{12}$, CO_2R^{12}, $C(O)SR^{12}$, $C(O)NR^{12}R^{13}$, $C(S)NR^{12}R^{13}$, $NR^{12}C(O)R^{13}$, $NR^{12}C(S)R^{13}$, $NR^{12}CO_2R^{13}$, $NR^{12}C(O)SR^{13}$, and a halogen, wherein:

p is an integer from 0 to 5;

R^{11} is a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl in which at least one hydrogen atom is optionally substituted with a substituent independently selected from the group consisting of a halogen, OH, OCH_3, NH_2, NO_2, SH, and CN; and

R^{12} and R^{13} are independently selected from the group consisting of H, an alkyl, an alkenyl, and an alkynyl;

R^4 is OH, =O (keto), NH_2, of $NHCH_3$, wherein, when R^4 is OH, it is optionally in the form of a pharmaceutically acceptable ester or prodrug, and when R^4 is NH_2, it is optionally an amide, a hydroxylamino, a carbamate, a urea,

an alkylamino, a dialkylamino, a protic salt, or a tetraalkylammonium salt;

R^5 is H, a C_1-C_6 alkyl radical, a C_2-C_6 alkenyl radical, or $(CH_2)_qR^{14}$, wherein q is an integer form 0 to 5, and R^{14} is a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl radical in which at least one hydrogen atom is optionally substituted with a substituent independently selected from the group consisting of a halogen, OH, OCH_3, NH_2, NO_2, SH, and CN;

W is C(O), C(S), S(O), or SO_2; and

R^6 is a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl radical in which at least one hydrogen atom is optionally substituted with a substituent independently selected from the group consisting of a halogen, OR^{15}, SR^{15}, $S(O)R^{15}$, SO_2R^{15}, $SO_2NR^{15}R^{16}$, $SO_2N(OH)R^{15}$, CN, $CR^{15}=NR^{16}$, $CR^{15}=N(OR^{16})$, N_3, NO_2, $NR^{15}R^{16}$, $N(OH)R^{15}$, $C(O)R^{15}$, $C(S)R^{15}$, CO_2R^{15}, $C(O)SR^{15}$, $C(O)NR^{15}R^{16}$, $C(S)NR^{15}R^{16}$, $C(O)N(OH)R^{15}$, $C(S)N(OH)R^{15}$, $NR^{15}C(O)R^{16}$, $NR^{15}C(S)R^{16}$, $N(OH)C(O)R^{15}$, $N(OH)C(S)R^{15}$, $NR^{15}CO_2R^{16}$, $N(OH)CO_2R^{15}$, $NR^{15}C(O)SR^{16}$, $NR^{15}C(O)NR^{16}R^{17}$, and $NR^{15}C(S)NR^{16}R^{17}$, $N(OH)C(O)NR^{15}R^{16}$, $N(OH)C(S)NR^{15}R^{16}$, $NR^{15}C(O)N(OH)R^{16}$, $NR^{15}C(S)N(OH)R^{16}$, $NR^{15}SO_2R^{16}$, $NHSO_2NR^{15}R^{16}$, $NR^{15}SO_2NHR^{16}$, $P(O)(OR^{15})(OR^{16})$, an alkyl, an alkoxy, an alkylthio, an alkylamino, a cycloalkyl, a cycloalkylalkyl, a heterocycloalkyl, a heterocycloalkylalkyl, an aryl, an aryloxy, an arylamino, an arylthio, an aralkyl, an aryloxyalkyl, an arylaminoalkyl, an aralkoxy, an (aryloxy)alkoxy, an (arylamino)alkoxy, an (arylthio)alkoxy, an aralkylamino, an (aryloxy)alkylamino, an (arylamino)alkylamino, an (arylthio)alkylamino, an aralkylthio, an (aryloxy)alkylthio, an (arylamino)alkylthio, an (arylthio)alkylthio, a heteroaryl, a heteroaryloxy, a heteroarylamino, a heteroarylthio, a

heteroaralkyl, a heteroaralkoxy, a heteroaralkylamino, and a heteroaralkylthio,

wherein R^{15}, R^{16}, and R^{17} are H, an unsubstituted alkyl, and an unsubstituted alkenyl,

wherein, when at least one hydrogen atom of R^6 is optionally substituted with a substituent other than a halogen, OR^{15}, SR^{15}, $S(O)R^{15}$, SO_2R^{15}, $SO_2NR^{15}R^{16}$, $SO_2N(OH)R^{15}$, CN, $CR^{15}=NR^{16}$, $CR^{15}=N(OR^{16})$, N_3, NO_2, $NR^{15}R^{16}$, $N(OH)R^{15}$, $C(O)R^{15}$, $C(S)R^{15}$, CO_2R^{15}, $C(O)SR^{15}$, $C(O)NR^{15}R^{16}$, $C(S)NR^{15}R^{16}$, $C(O)N(OH)R^{15}$, $C(S)N(OH)R^{15}$, $NR^{15}C(O)R^{16}$, $NR^{15}C(S)R^{16}$, $N(OH)C(O)R^{15}$, $N(OH)C(S)R^{15}$, $NR^{15}CO_2R^{16}$, $N(OH)CO_2R^{15}$, $NR^{15}C(O)SR^{16}$, $NR^{15}C(O)NR^{16}R^{17}$, $NR^{15}C(S)NR^{16}R^{17}$, $N(OH)C(O)NR^{15}R^{16}$, $N(OH)C(S)NR^{15}R^{16}$, $NR^{15}C(O)N(OH)R^{16}$, $NR^{15}C(S)N(OH)R^{16}$, $NR^{15}SO_2R^{16}$, $NHSO_2NR^{15}R^{16}$, $NR^{15}SO_2NHR^{16}$, or $P(O)(OR^{15})(OR^{16})$, then at least one hydrogen atom on said substituent is optionally substituted with a halogen, OR^{15}, SR^{15}, $S(O)R^{15}$, SO_2R^{15}, $SO_2NR^{15}R^{16}$, $SO_2N(OH)R^{15}$, CN, $CR^{15}=NR^{16}$, $CR^{15}=N(OR^{16})$, N_3, NO_2, $NR^{15}R^{16}$, $N(OH)R^{15}$, $C(O)R^{15}$, $C(S)R^{15}$, CO_2R^{15}, $C(O)SR^{15}$, $C(O)NR^{15}R^{16}$, $C(S)NR^{15}R^{16}$, $C(O)N(OH)R^{15}$, $C(S)N(OH)R^{15}$, $NR^{15}C(O)R^{16}$, $NR^{15}C(S)R^{16}$, $N(OH)C(O)R^{15}$, $N(OH)C(S)R^{15}$, $NR^{15}CO_2R^{16}$, $N(OH)CO_2R^{15}$, $NR^{15}C(O)SR^{16}$, $NR^{15}C(O)NR^{16}R^{17}$, $NR^{15}C(S)NR^{16}R^{17}$, $N(OH)C(O)NR^{15}R^{16}$, $N(OH)C(S)NR^{15}R^{16}$, $NR^{15}C(O)N(OH)R^{16}$, $NR^{15}C(S)N(OH)R^{16}$, $NR^{15}SO_2R^{16}$, $NHSO_2NR^{15}R^{16}$, $NR^{15}SO_2NHR^{16}$, or $P(O)(OR^{15})(OR^{16})$;

wherein the compound inhibits a retroviral protease, more particularly a multidrug-resistant retroviral protease, more particularly a multidrug-resistant HIV protease. Optionally, R^5 and R^6 are covalently joined together, such that R^5 and R^6 together comprise a 12 to 18 membered ring, with or without a heteroatom (e.g., N, O, or S) within the ring, which ring includes the N-W bond of Formula (I).

Also provided is a pharmaceutical composition comprising a multidrug-resistant retroviral protease-inhibiting amount of a compound of the present invention (or a pharmaceutically acceptable salt, a prodrug, or an ester thereof) and a pharmaceutically acceptable carrier.

The present invention further provides a method of inhibiting the protease of a multidrug-resistant retrovirus in a mammal infected with a protease-producing, multidrug-resistant retrovirus. The method comprises administering a multidrug-resistant, retroviral protease-inhibiting effective amount of a compound of the present invention, so as to inhibit proliferation of the retrovirus in the mammal.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 illustrates the synthesis of a particular sulfonamide isostere core of a compound of the present invention.

Figure 2 illustrates the synthesis of a bis-tetrahydrofuran ligand and the optical resolution thereof.

Fig. 3A illustrates the synthesis of a multidrug-resistant retroviral protease inhibitor of the present invention via coupling of a bis-tetrahydrofuran ligand to a sulfonamide isostere of the present invention.

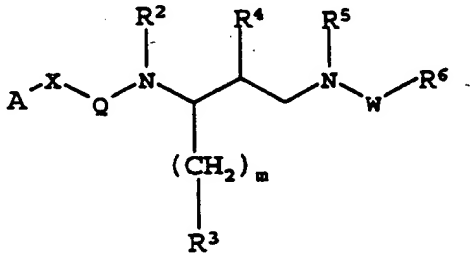
Fig. 3B illustrates the synthesis of a multidrug-resistant retroviral protease inhibitor of the present invention via coupling of a bis-tetrahydrofuran ligand to a sulfonamide isostere of the present invention.

Figure 4 illustrates generally the present method of synthesizing a multidrug-resistant inhibitor of the present invention.

Figures 5A-5D illustrate the structures of particular compounds that were tested against various drug-resistant HIV mutants.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

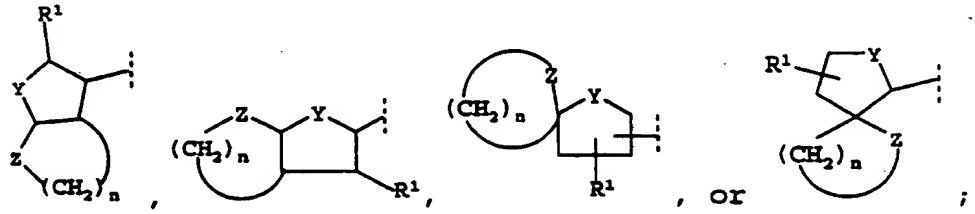
The present invention provides a retroviral protease-inhibiting compound represented by the formula:



(I),

or a pharmaceutically acceptable salt, a prodrug, or an ester thereof, wherein:

A is a group of the formula:



;

R^1 is H or an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkylalkyl, an aryl, an aralkyl, a heterocycloalkyl, a heterocycloalkylalkyl, a heteroaryl, or a heteroaralkyl radical, in which at least one hydrogen atom is optionally substituted with a substituent independently selected from the group consisting of OR^7,

SR^7, CN, NO_2, N_3, and a halogen, wherein R^7 is H, an alkyl, an alkenyl, or an alkynyl;

Y and Z are the same or different and are independently selected from the group consisting of CH_2, O, S, SO, SO_2, NR^8, $R^8C(O)N$, $R^8C(S)N$, $R^8OC(O)N$, $R^8OC(S)N$, $R^8SC(O)N$, $R^8R^9NC(O)N$, and $R^8R^9NC(S)N$, wherein R^8 and R^9 are independently selected from the group consisting of H, an alkyl, an alkenyl, and an alkynyl;

n is an integer from 1 to 5;

X is a covalent bond, CHR^{10}, $CHR^{10}CH_2$, CH_2CHR^{10}, O, NR^{10}, or S, wherein R^{10} is H, an alkyl, an alkenyl, or an alkynyl;

Q is C(O), C(S), or SO_2;

R^2 is H, an alkyl, an alkenyl, or an alkynyl;

m is an integer from 0 to 6;

R^3 is a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl in which at least one hydrogen atom is optionally substituted with a substituent independently selected from the group consisting of H, alkyl, $(CH_2)_pR^{11}$, OR^{12}, SR^{12}, CN, N_3, NO_2, $NR^{12}R^{13}$, $C(O)R^{12}$, $C(S)R^{12}$, CO_2R^{12}, $C(O)SR^{12}$, $C(O)NR^{12}R^{13}$, $C(S)NR^{12}R^{13}$, $NR^{12}C(O)R^{13}$, $NR^{12}C(S)R^{13}$, $NR^{12}CO_2R^{13}$, $NR^{12}C(O)SR^{13}$, and a halogen, wherein:

p is an integer from 0 to 5;

R^{11} is a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl in which at least one hydrogen atom is optionally substituted with a substituent independently selected from the group consisting of a halogen, OH, OCH_3, NH_2, NO_2, SH, and CN; and

R^{12} and R^{13} are independently selected from the group consisting of H, an alkyl, an alkenyl, and an alkynyl;

R^4 is OH, =O (keto), or NH_2, wherein, when R^4 is OH, it is optionally in the form of a pharmaceutically acceptable

ester or prodrug, and when R^4 is NH_2, it is optionally an amide, a hydroxylamino, a carbamate, a urea, an alkylamino, a dialkylamino, a protic salt, or a tetraalkylammonium salt;

R^5 is H, a C_1-C_6 alkyl radical, a C_2-C_6 alkenyl radical, or $(CH_2)_qR^{14}$, wherein q is an integer form 0 to 5, and R^{14} is a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl radical in which at least one hydrogen atom is optionally substituted with a substituent independently selected from the group consisting of a halogen, OH, OCH_3, NH_2, NO_2, SH, and CN;

W is C(O), C(S), S(O), or SO_2; and

R^6 is a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl radical in which at least one hydrogen atom is optionally substituted with a substituent independently selected from the group consisting of a halogen, OR^{15}, SR^{15}, $S(O)R^{15}$, SO_2R^{15}, $SO_2NR^{15}R^{16}$, $SO_2N(OH)R^{15}$, CN, $CR^{15}=NR^{16}$, $CR^{15}=N(OR^{16})$, N_3, NO_2, $NR^{15}R^{16}$, $N(OH)R^{15}$, $C(O)R^{15}$, $C(S)R^{15}$, CO_2R^{15}, $C(O)SR^{15}$, $C(O)NR^{15}R^{16}$, $C(S)NR^{15}R^{16}$, $C(O)N(OH)R^{15}$, $C(S)N(OH)R^{15}$, $NR^{15}C(O)R^{16}$, $NR^{15}C(S)R^{16}$, $N(OH)C(O)R^{15}$, $N(OH)C(S)R^{15}$, $NR^{15}CO_2R^{16}$, $N(OH)CO_2R^{15}$, $NR^{15}C(O)SR^{16}$, $NR^{15}C(O)NR^{16}R^{17}$, and $NR^{15}C(S)NR^{16}R^{17}$, $N(OH)C(O)NR^{15}R^{16}$, $N(OH)C(S)NR^{15}R^{16}$, $NR^{15}C(O)N(OH)R^{16}$, $NR^{15}C(S)N(OH)R^{16}$, $NR^{15}SO_2R^{16}$, $NHSO_2NR^{15}R^{16}$, $NR^{15}SO_2NHR^{16}$, $P(O)(OR^{15})(OR^{16})$, an alkyl, an alkoxy, an alkylthio, an alkylamino, a cycloalkyl, a cycloalkylalkyl, a heterocycloalkyl, a heterocycloalkylalkyl, an aryl, an aryloxy, an arylamino, an arylthio, an aralkyl, an aryloxyalkyl, an arylaminoalkyl, an aralkoxy, an (aryloxy)alkoxy, an (arylamino)alkoxy, an (arylthio)alkoxy, an aralkylamino, an (aryloxy)alkylamino, an (arylamino)alkylamino, an (arylthio)alkylamino, an aralkylthio, an (aryloxy)alkylthio, an

(arylamino)alkylthio, an (arylthio)alkylthio, a heteroaryl, a heteroaryloxy, a heteroarylamino, a heteroarylthio, a heteroaralkyl, a heteroaralkoxy, a heteroaralkylamino, and a heteroaralkylthio,

wherein R^{15}, R^{16}, and R^{17} are H, an unsubstituted alkyl, and an unsubstituted alkenyl,

wherein, when at least one hydrogen atom of R^6 is optionally substituted with a substituent other than a halogen, OR^{15}, SR^{15}, $S(O)R^{15}$, SO_2R^{15}, $SO_2NR^{15}R^{16}$, $SO_2N(OH)R^{15}$, CN, $CR^{15}=NR^{16}$, $CR^{15}=N(OR^{16})$, N_3, NO_2, $NR^{15}R^{16}$, $N(OH)R^{15}$, $C(O)R^{15}$, $C(S)R^{15}$, CO_2R^{15}, $C(O)SR^{15}$, $C(O)NR^{15}R^{16}$, $C(S)NR^{15}R^{16}$, $C(O)N(OH)R^{15}$, $C(S)N(OH)R^{15}$, $NR^{15}C(O)R^{16}$, $NR^{15}C(S)R^{16}$, $N(OH)C(O)R^{15}$, $N(OH)C(S)R^{15}$, $NR^{15}CO_2R^{16}$, $N(OH)CO_2R^{15}$, $NR^{15}C(O)SR^{16}$, $NR^{15}C(O)NR^{16}R^{17}$, $NR^{15}C(S)NR^{16}R^{17}$, $N(OH)C(O)NR^{15}R^{16}$, $N(OH)C(S)NR^{15}R^{16}$, $NR^{15}C(O)N(OH)R^{16}$, $NR^{15}C(S)N(OH)R^{16}$, $NR^{15}SO_2R^{16}$, $NHSO_2NR^{15}R^{16}$, $NR^{15}SO_2NHR^{16}$, or $P(O)(OR^{15})(OR^{16})$, then at least one hydrogen atom on said substituent is optionally substituted with a halogen, OR^{15}, SR^{15}, $S(O)R^{15}$, SO_2R^{15}, $SO_2NR^{15}R^{16}$, $SO_2N(OH)R^{15}$, CN, $CR^{15}=NR^{16}$, $CR^{15}=N(OR^{16})$, N_3, NO_2, $NR^{15}R^{16}$, $N(OH)R^{15}$, $C(O)R^{15}$, $C(S)R^{15}$, CO_2R^{15}, $C(O)SR^{15}$, $C(O)NR^{15}R^{16}$, $C(S)NR^{15}R^{16}$, $C(O)N(OH)R^{15}$, $C(S)N(OH)R^{15}$, $NR^{15}C(O)R^{16}$, $NR^{15}C(S)R^{16}$, $N(OH)C(O)R^{15}$, $N(OH)C(S)R^{15}$, $NR^{15}CO_2R^{16}$, $N(OH)CO_2R^{15}$, $NR^{15}C(O)SR^{16}$, $NR^{15}C(O)NR^{16}R^{17}$, $NR^{15}C(S)NR^{16}R^{17}$, $N(OH)C(O)NR^{15}R^{16}$, $N(OH)C(S)NR^{15}R^{16}$, $NR^{15}C(O)N(OH)R^{16}$, $NR^{15}C(S)N(OH)R^{16}$, $NR^{15}SO_2R^{16}$, $NHSO_2NR^{15}R^{16}$, $NR^{15}SO_2NHR^{16}$, or $P(O)(OR^{15})(OR^{16})$;

wherein the compound of the present invention inhibits a retroviral protease, more particularly a multidrug-resistant retroviral protease, more particularly a multidrug-resistant HIV protease. Optionally, R^5 and R^6 are covalently joined together, such that R^5 and R^6 together comprise a 12 to 18 membered ring, with or without a

heteroatom (e.g., N, O, or S) within the ring, which ring includes the N-W bond of Formula (I).

As utilized herein, the term "alkyl" means a straight-chain or branched-chain alkyl radical containing from about 1 to about 20 carbon atoms chain, preferably from about 1 to about 10 carbon atoms, more preferably from about 1 to about 8 carbon atoms, still more preferably from about 1 to about 6 carbon atoms. Examples of such substituents include methyl, ethyl, propyl, isopropyl, *n*-butyl, *sec*-butyl, isobutyl, *tert*-butyl, pentyl, isoamyl, hexyl, octyl, dodecanyl, and the like.

The term "alkenyl" means a straight-chain or branched-chain alkenyl radical having one or more double bonds and containing from about 2 to about 20 carbon atoms chain, preferably from about 2 to about 10 carbon atoms, more preferably from about 2 to about 8 carbon atoms, still more preferably from about 2 to about 6 carbon atoms. Examples of such substituents include vinyl, allyl, 1,4-butadienyl, isopropenyl, and the like.

The term "alkynyl" means a straight-chain or branched-chain alkynyl radical having one or more triple bonds and containing from about 2 to about 20 carbon atoms chain, preferably from about 2 to about 10 carbon atoms, more preferably from about 2 to about 8 carbon atoms, still more preferably from about 2 to about 6 carbon atoms. Examples of such radicals include ethynyl, propynyl (propargyl), butynyl, and the like.

The term "alkoxy" means an alkyl ether radical, wherein the term "alkyl" is defined as above. Examples of alkoxy radicals include methoxy, ethoxy, *n*-propoxy, isopropoxy, *n*-butoxy, isobutoxy, *sec*-butoxy, *tert*-butoxy, hexanoxy, and the like.

The term "alkylthio" means an alkyl thioether radical, wherein the term "alkyl" is defined as above. Examples of alkylthio radicals include methylthio (SCH_3), ethylthio (SCH_2CH_3), *n*-propylthio, isopropylthio, *n*-butylthio, isobutylthio, *sec*-butylthio, *tert*-butylthio, *n*-hexylthio, and the like.

The term "alkylamino" means an alkyl amine radical, wherein the term "alkyl" is defined as above. Examples of alkylamino radicals include methylamino ($NHCH_3$), ethylamino ($NHCH_2CH_3$), *n*-propylamino, isopropylamino, *n*-butylamino, isobutylamino, *sec*-butylamino, *tert*-butylamino, *n*-hexylamino, and the like.

The term "cycloalkyl" means a monocyclic or a polycyclic alkyl radical defined by one or more alkyl carbocyclic rings, which can be the same or different when the cycloalkyl is a polycyclic radical having 3 to about 10 carbon atoms in the carbocyclic skeleton in each ring, preferably about 4 to about 7 carbon atoms, more preferably 5 to 6 carbons atoms. Examples of monocyclic cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclodecyl, and the like. Examples of polycyclic cycloalkyl radicals include decahydronaphthyl, bicyclo[5.4.0]undecyl, adamantyl, and the like.

The term "cycloalkylalkyl" means an alkyl radical as defined herein, in which at least one hydrogen atom on the alkyl radical is replaced by a cycloalkyl radical as defined herein. Examples of cycloalkylalkyl radicals include cyclohexylmethyl, 3-cyclopentylbutyl, and the like.

The term "heterocycloalkyl" means a cycloalkyl radical as defined herein (including polycyclics), wherein at least one carbon which defines the carbocyclic skeleton is substituted with a heteroatom such as, for example, O, N, or

S, optionally comprising one or more double bond within the ring, provided the ring is not heteroaryl as defined herein. The heterocycloalkyl preferably has 3 to about 10 atoms (members) in the carbocyclic skeleton of each ring, preferably about 4 to about 7 atoms, more preferably 5 to 6 atoms. Examples of heterocycloalkyl radicals include epoxy, aziridyl, oxetanyl, tetrahydrofuranyl, dihydrofuranyl, piperadyl, piperidinyl, pyperazyl, piperazinyl, pyranyl, morpholinyl, and the like.

The term "heterocycloalkylalkyl" means an alkyl radical as defined herein, in which at least one hydrogen atom on the alkyl radical is replace by a heterocycloalkyl radical as defined herein. Examples of heterocycloalkylalkyl radicals include 2-morpholinomethyl, 3-(4-morpholino)-propyl, 4-(2-tetrahydrofuranyl)-butyl, and the like.

The term "aryl" refers to an aromatic carbocyclic radical, as commonly understood in the art, and includes monocyclic and polycyclic aromatics such as, for example, phenyl and naphthyl radicals, optionally substituted with one or more substituents selected from the group consisting of a halogen, an alkyl, alkoxy, amino, cyano, nitro, and the like.

The term "aryloxy" means aryl as defined herein, wherein a hydrogen atom is replaced by an oxygen. Examples of aryloxy radicals include phenoxy, naphthoxy, 4-flourophenoxy, and the like.

The term "arylamino" means aryl as defined herein, wherein a hydrogen atom is replaced by an amine. Examples of arylamino radicals include phenylamino, naphthylamino, 3-nitrophenylamino, 4-aminophenylamino, and the like.

The term "arylthio" means aryl as defined herein, wherein a hydrogen atom is replaced by a sulfur atom.

Examples of arylthio radicals include phenylthio, naphthylthio, 3-nitrophenylthio, 4-thiophenylthio, and the like.

The term "aralkyl" means alkyl as defined herein, wherein an alkyl hydrogen atom is replaced by an aryl as defined herein. Examples of aralkyl radicals include benzyl, phenethyl, 3-(2-naphthyl)-butyl, and the like.

The term "aryloxyalkyl" means alkyl as defined herein, wherein an alkyl hydrogen atom is replaced by an aryloxy as defined herein. Examples of aryloxyalkyl radicals include phenoxyethyl, 4-(3-aminophenoxy)-1-butyl, and the like.

The term "arylaminoalkyl" means alkyl as defined herein, wherein an alkyl hydrogen atom is replaced by an arylamino as defined herein. Examples of arylaminoalkyl radicals include phenylaminoethyl, 4-(3-methoxyphenylamino)-1-butyl, and the like.

The term "aralkoxy" means alkoxy as defined herein, wherein an alkyl hydrogen atom is replaced by an aryl as defined herein. Examples of aralkoxy radicals include 2-phenylethoxy, 2-phenyl-1-propoxy, and the like.

The term "(aryloxy)alkoxy" means alkoxy as defined herein, wherein an alkyl hydrogen atom is replaced by an aryloxy as defined herein. Examples of (aryloxy)alkoxy radicals include 2-phenoxyethoxy, 4-(3-aminophenoxy)-1-butoxy, and the like.

The term "(arylamino)alkoxy" means alkoxy as defined herein, wherein an alkyl hydrogen atom is replaced by an arylamino as defined herein. Examples of (arylamino)alkoxy radicals include 2-(phenylamino)-ethoxy, 2-(2-naphthylamino)-1-butoxy, and the like.

The term "(arylthio)alkoxy" means alkoxy as defined herein, wherein an alkyl hydrogen atom is replaced by an

arylthio as defined herein. Examples of (arylthio)alkoxy radicals include 2-(phenylthio)-ethoxy, and the like.

The term "aralkylamino" means alkylamino as defined herein, wherein an alkyl hydrogen atom is replaced by an aryl as defined herein. Examples of aralkylamino radicals include 2-phenethylamino, 4-phenyl-*n*-butylamino, and the like.

The term "(aryloxy)alkylamino" means alkylamino as defined herein, wherein an alkyl hydrogen atom is replaced by an aryloxy as defined herein. Examples of (aryloxy)alkylamino radicals include 3-phenoxy-*n*-propylamino, 4-phenoxybutylamino, and the like.

The term "(arylamino)alkylamino" means alkylamino as defined herein, wherein an alkyl hydrogen atom is replaced by an arylamino as defined herein. Examples of (arylamino)alkylamino radicals include 3-(naphthylamino)-1-propylamino, 4-(phenylamino)-1-butylamino, and the like.

The term "(arylthio)alkylamino" means alkylamino as defined herein, wherein an alkyl hydrogen atom is replaced by an arylthio as defined herein. Examples of (arylthio)alkylamino radicals include 2-(phenylthio)-ethylamino, and the like.

The term "aralkylthio" means alkylthio as defined herein, wherein an alkyl hydrogen atom is replaced by an aryl as defined herein. Examples of aralkylthio radicals include 3-phenyl-2-propylthio, 2-(2-naphthyl)-ethylthio, and the like.

The term "(aryloxy)alkylthio" means alkylthio as defined herein, wherein an alkyl hydrogen atom is replaced by an aryloxy as defined herein. Examples of (aryloxy)alkylthio radicals include 3-phenoxypropylthio, 4-(2-fluorophenoxy)- butylthio, and the lik .

The term "(arylamino)alkylthio" means alkylthio as defined herein, wherein an alkyl hydrogen atom is replaced by an arylamino as defined herein. Examples of (arylamino)alkylthio radicals include 2-(phenylamino)-ethylthio, 3-(2-naphthylamino)-*n*-propylthio, and the like.

The term "(arylthio)alkylthio" means alkylthio as defined herein, wherein an alkyl hydrogen atom is replaced by an arylthio as defined herein. Examples of (arylthio)alkylthio radicals include 2-(naphthylthio)-ethylthio, 3-(phenylthio)-propylthio, and the like.

The term "heteroaryl" means a radical defined by an aromatic heterocyclic ring as commonly understood in the art, including monocyclic radicals such as, for example, imidazole, thiazole, pyrazole, pyrrole, furane, pyrazoline, thiophene, oxazole, isoxazol, pyridine, pyridone, pyrimidine, pyrazine, and triazine radicals, and also including polycyclics such as, for example, quinoline, isoquinoline, indole, and benzothiazole radicals, which heteroaryl radicals are optionally substituted with one or more substituents selected from the group consisting of a halogen, an alkyl, alkoxy, amino, cyano, nitro, and the like. It will be appreciated that the heterocycloalkyl and heteroaryl substituents can be coupled to the compounds of the present invention via a heteroatom, such as nitrogen (e.g., 1-imidazolyl).

The term "heteroaryloxy" means heteroaryl as defined herein, wherein a hydrogen atom on the heteroaryl ring is replaced by an oxygen. Heteroaryloxy radicals include, for example, 4-pyridyloxy, 5-quinolyloxy, and the like.

The term "heteroarylamino" means heteroaryl as defined herein, wherein a hydrogen atom on the heteroaryl ring is

replaced by an nitrogen. Heteroa
for example, 4-thiazolylamino, 2-

The term "heteroarylthio" me
herein, wherein a hydrogen atom o
replaced by a sulfur. Heteroaryl
example, 3-pyridylthio, 3-quinoly
and the like.

The term "heteroaralkyl" mea
wherein an alkyl hydrogen atom is
as defined herein. Examples of he
include 2-pyridylmethyl, 3-(4-thia
like.

The term "heteroaralkoxy" mea
herein, wherein an alkyl hydrogen a
heteroaryl as defined herein. Exam
radicals include 2-pyridylmethoxy,
and the like.

The term "heteroaralkylamino"
defined herein, wherein an alkyl hyc
by a heteroaryl as defined herein.
heteroaralkylamino radicals include
(2-furanyl)-propylamino, and the lik

The term "heteroaralkylthio" m
defined herein, wherein an alkyl hyd
by a heteroaryl as defined herein.
heteroaralkylthio radicals include 3
(4-thiazolyl)-propylthio, and the lik

In the compounds of the present
preferred that R^1 is H or an alkyl, a
cycloalkyl, a cycloalkylalkyl, an ary
heterocycloalkyl, a heterocycloalkyla
a heteroaralkyl radical, in which at

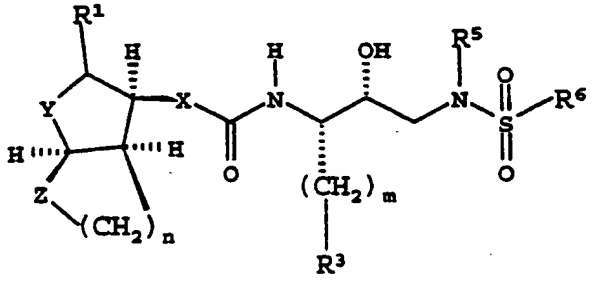
atom is optionally substituted with a substituent independently selected from the group consisting of OR^7, SR^7, CN, NO_2, N_3, and a halogen, wherein R^7 is H, an unsubstituted alkyl, or an unsubstituted alkenyl; Y and Z are the same or different and are independently selected from the group consisting of CH_2, O, S, SO, SO_2, NR^8, $R^8C(O)N$, $R^8C(S)N$, $R^8OC(O)N$, $R^8OC(S)N$, $R^8SC(O)N$, $R^8R^9NC(O)N$, and $R^8R^9NC(S)N$, wherein R^8 and R^9 are independently selected from the group consisting of H, an unsubstituted alkyl, and an unsubstituted alkenyl; X is a covalent bond, CHR^{10}, $CHR^{10}CH_2$, CH_2CHR^{10}, O, NR^{10}, or S, wherein R^{10} is H, an unsubstituted alkyl, or an unsubstituted alkenyl; R^2 is H, a C_1-C_6 alkyl radical, or a C_2-C_6 alkenyl radical; R^{12} and R^{13}, as defined with respect to R^3, are independently selected from the group consisting of H, an unsubstituted alkyl, and an unsubstituted alkenyl radical; R^4 is OH, NH_2, or $NHCH_3$; W is C(O), C(S), or SO_2; and R^6 is a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl radical in which at least one hydrogen atom is optionally substituted with a substituent independently selected from the group consisting of a halogen, OR^{15}, SR^{15}, CN, N_3, NO_2, $NR^{15}R^{16}$, $C(O)R^{15}$, $C(S)R^{15}$, CO_2R^{15}, $C(O)SR^{15}$, $C(O)NR^{15}R^{16}$, $C(S)NR^{15}R^{16}$, $NR^{15}C(O)R^{16}$, $NR^{15}C(S)R^{16}$, $NR^{15}CO_2R^{16}$, $NR^{15}C(O)SR^{16}$, $NR^{15}C(O)NR^{16}R^{17}$, and $NR^{15}C(S)NR^{16}R^{17}$, an alkyl, an alkoxy, an alkylthio, an alkylamino, a cycloalkyl, a cycloalkylalkyl, a heterocycloalkyl, a heterocycloalkylalkyl, an aryl, an aryloxy, an arylamino, an arylthio, an aralkyl, an aryloxyalkyl, an arylaminoalkyl, an aralkoxy, an (aryloxy)alkoxy, an (arylamino)alkoxy, an (arylthio)alkoxy, an aralkylamino, an (aryloxy)alkylamino, an (arylamino)alkylamino, an (arylthio)alkylamino, an aralkylthio, an (aryloxy)alkylthio, an

(arylamino)alkylthio, an (arylthio)alkylthio, a heteroaryl, a heteroaryloxy, a heteroarylamino, a heteroarylthio, a heteroaralkyl, a heteroaralkoxy, a heteroaralkylamino, and a heteroaralkylthio, wherein R^{15}, R^{16}, and R^{17} are H, an unsubstituted alkyl, and an unsubstituted alkenyl, such that when at least one hydrogen atom of R^6 is optionally substituted with a substituent other than a halogen, OR^{15}, SR^{15}, CN, N_3, NO_2, $NR^{15}R^{16}$, $C(O)R^{15}$, $C(S)R^{15}$, CO_2R^{15}, $C(O)SR^{15}$, $C(O)NR^{15}R^{16}$, $C(S)NR^{15}R^{16}$, $NR^{15}C(O)R^{16}$, $NR^{15}C(S)R^{16}$, $NR^{15}CO_2R^{16}$, $NR^{15}C(O)SR^{16}$, $NR^{15}C(O)NR^{16}R^{17}$, or $NR^{15}C(S)NR^{16}R^{17}$, at least one hydrogen atom on said substituent attached to R^6 is optionally substituted with a halogen, OR^{15}, SR^{15}, CN, N_3, NO_2, $NR^{15}R^{16}$, $C(O)R^{15}$, $C(S)R^{15}$, CO_2R^{15}, $C(O)SR^{15}$, $C(O)NR^{15}R^{16}$, $C(S)NR^{15}R^{16}$, $NR^{15}C(O)R^{15}$, $NR^{15}C(S)R^{16}$, $NR^{15}CO_2R^{16}$, $NR^{15}C(O)SR^{16}$, $NR^{15}C(O)NR^{16}R^{17}$, or $NR^{15}C(S)NR^{16}R^{17}$.

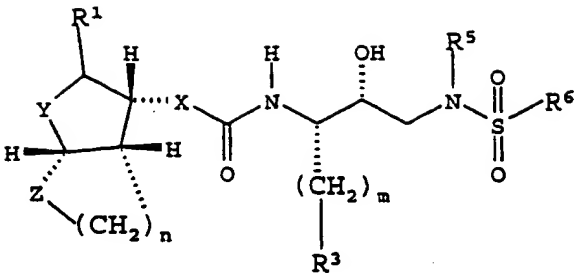
It is further preferred that when R^1 is an alkyl or an alkenyl radical (i.e., an alkyl or an alkenyl substituent), then it is a C_1-C_6 alkyl or, in the case when R^1 is an alkenyl, it is a C_2-C_6 alkenyl. When R^1 is a monocyclic substituent such as, for example, a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl, it preferably comprises 4-7 members in the ring that defines the monocyclic skeleton. When R^7, R^8 or R^9 is an unsubstituted alkyl, it is preferably a C_1-C_6 unsubstituted alkyl; and when R^7, R^8 or R^9 is an unsubstituted alkenyl, it is preferably a C_2-C_6 unsubstituted alkenyl. The ring defined by R^3 preferably comprises 4-7 members or, in the case of polycyclics, each ring comprises 4-7 members. When R^3 is $(CH_2)_pR^{11}$, the ring defined by R^{11} preferably comprises 4-7 members, or, in the case of polycyclics, each ring comprises 4-7 members. When either of R^{12} or R^{13} is an unsubstituted alkyl, it is preferably a C_1-C_6 unsubstituted

alkyl, and when either of R^{12} or R^{13} is an unsubstituted alkenyl, it is a C_2-C_6 unsubstituted alkyl. When R^{14} is a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl, the ring defined by R^{14} preferably comprises 4-7 members, or, in the case of polycyclics, each ring comprises 4-7 members. When R^6 is a cycloalkyl, a heterocycloalkyl, aryl, or a heteroaryl, the ring defined by R^6 preferably comprises 4-7 members, or, in the case of polycyclics, each ring comprises 4-7 members, and when R^6 is substituted with a substituent that is an alkyl, an alkylthio, or an alkylamino, it is preferred that the substituent comprises from one to six carbon atoms, and when R^6 is substituted with a substituent that is a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl, the ring defined by the substituent preferably comprises 4-7 members or, in the case of polycyclics, each ring comprises 4-7 members.

In a preferred embodiment, the compound of the present invention is represented by Formula (I), wherein Q is C(O), R^2 is H, and W is C(O) or SO_2. In a further preferred embodiment, Q is C(O), R^2 is H, R^4 is OH, W is SO_2, and the stereochemical orientation of the asymmetric centers is represented by formula (IA) or (IB) below:

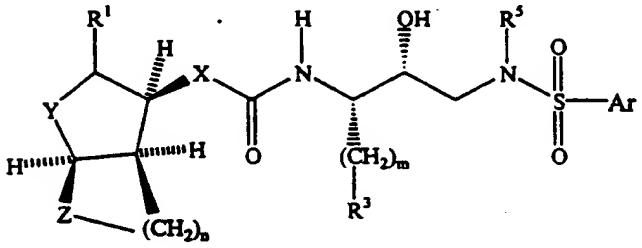


(IA) or

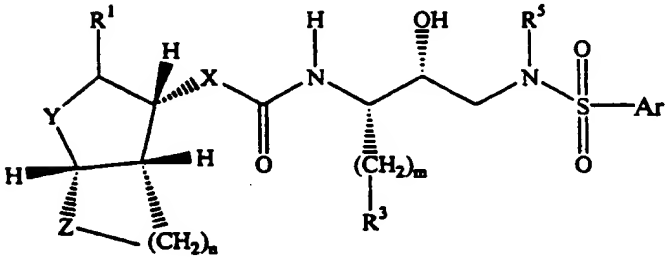


(IB).

It is further preferred that R^6 is a monocyclic substituent, preferably an aromatic ring, which is preferably a substituted benzene ring, as illustrated by the formula:



(IC) or

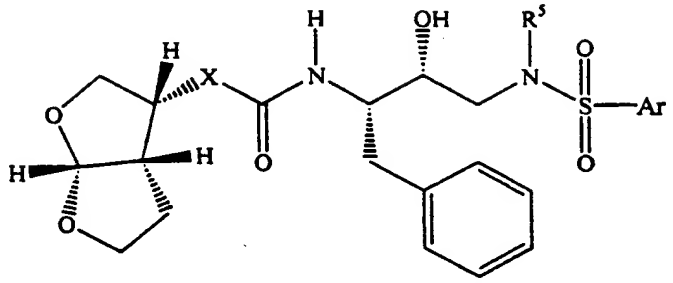


(ID),

wherein, Ar is a phenyl which is optionally substituted with a substituent selected from the group consisting of methyl, amino, hydroxy, methoxy, methylthio, hydroxymethyl, aminomethyl, and methoxymethyl.

In a preferred series, Y and Z are oxygen atoms, n is 2, the resulting bis-tetrahydrofuranyl ring system has the stereochemical orientation illustrated in Formula (ID)

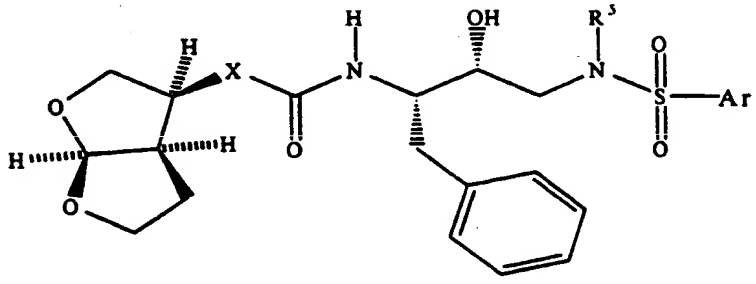
above, m is 1, and R^3 is phenyl, in which case the compound is represented by the formula:



(IE).

It is further preferred that X is an oxygen, R^5 is isobutyl, and that Ar is a phenyl which is optionally substituted with a substituent selected from the group consisting of methyl, amino, hydroxy, methoxy, methylthio, hydroxymethyl, aminomethyl, and methoxymethyl.

In another preferred series, Y and Z are oxygen atoms, n is 2, the resulting bis-tetrahydrofuranyl ring system has the stereochemical orientation illustrated in Formula (1C) above, m is 1, and R^3 is phenyl, in which case the compound is represented by the formula:



(1F),

wherein, Ar is a phenyl which is optionally substituted with a substituent selected from the group consisting of methyl, amino, hydroxy, methoxy, methylthio, hydroxymethyl, aminomethyl, and methoxymethyl. When the compound of the present invention is a compound of Formula (IE) or (IF), wherein Ar is a phenyl that is optionally substituted with

a substituent selected from the group consisting of methyl, amino, hydroxy, methoxy, methylthio, hydroxymethyl, aminomethyl, and methoxymethyl, it is further preferred that X is an oxygen. Still more preferably, X is oxygen and R^5 is isobutyl. The Ar substituent includes phenyl substituents that are substituted at the para position, the ortho position, and/or the meta position. Examples of compounds substituted with suitable Ar substituents are shown in Table 4, and in Figures 3 and 5A-5D.

In accordance with the present invention, there is provided a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a retroviral protease-inhibiting, particularly a multidrug-resistant retroviral protease-inhibiting, effective amount of at least one compound of the present invention, alone or in combination with another antiretroviral compound such as, for example, a wild-type HIV protease inhibitor, a mutant HIV retroviral protease inhibitor, or a reverse transcriptase inhibitor. Generally, the pharmaceutical composition of the present invention comprises a multidrug-resistant retroviral protease-inhibiting effective amount of at least one compound of Formula (I), as disclosed herein, and a pharmaceutically acceptable carrier. In a preferred embodiment, the pharmaceutical composition of the present invention comprises a multidrug-resistant retroviral protease-inhibiting effective amount of at least one compound of Formula (IA) or Formula (IB), or a pharmaceutically acceptable salt, prodrug, or ester thereof, and a pharmaceutically acceptable carrier. In a further preferred embodiment, the present pharmaceutical composition comprises a multidrug-resistant retroviral protease-inhibiting effective amount of at least one

compound of Formula (IC) or Formula (ID), or a pharmaceutically acceptable salt, prodrug, or ester thereof, and a pharmaceutically acceptable carrier. In a highly preferred embodiment, the present pharmaceutical composition comprises a multidrug-resistant retroviral protease-inhibiting effective amount of at least one compound of Formula (IE), and pharmaceutically acceptable salts, prodrugs, and esters thereof, and a pharmaceutically acceptable carrier. Pharmaceutically acceptable carriers are well-known to those who are skilled in the art. The choice of a carrier will be determined in part by the particular composition, as well as by the particular mode of administration. Accordingly, there are a wide variety of suitable formulations of the pharmaceutical compositions of the present invention.

The pharmaceutical compositions of the present invention may be in a form suitable for oral use such as, for example, tablets, troches, lozenges, aqueous or oily suspensions or solutions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs. Compositions intended for oral use may be prepared according to any method known in the art form the manufacture of pharmaceutical compositions, and such compositions can contain one or more agents such as, for example, sweetening agents, flavoring agents, coloring agents, and preserving agents in order to provide a pharmaceutically elegant and/or palatable preparation. Tablets can contain the active ingredient in admixture with non-toxic pharmaceutically acceptable excipients which are suitable for manufacture of tablets. Such excipients can be, for example, inert diluents such as, for example, calcium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and

disintegrating agents such as, for example, maize starch or alginic acid; binding agents such as, for example, starch, gelatine or acacia, and lubricating agents such as, for example, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

Formulations for oral use also can be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert solid diluent, for example calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example arachis oil, peanut oil, liquid paraffin or olive oil.

Aqueous suspensions typically contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example, sodium carboxymethyl cellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gam acacia; dispersing or wetting agents may be a natural-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation

products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyoxyethylene sorbitan mono-oleate. The aqueous suspensions also can contain one or more preservatives, for example, ethyl or n-propyl p-hydroxy benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents such as, for example, sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oil suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions can be preserved by the addition of an antioxidant such as, for example, ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, also may be present.

The pharmaceutical compositions of the present invention also can be in the form of oil-in-water emulsions. The oily phase can be a vegetable oil, for example, olive oil or arachis oils, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents

may be naturally-occurring gums, for example gum acacia or gum tragacantn, naturally-occurring phosphatides, for example soya bean lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan mono-oleate, and condensation products of the said partial esters and ethylene oxide, for example polyoxyethylene sorbitan mono-oleate. The emulsions also can contain sweetening and flavoring agents.

The pharmaceutical compositions of the present invention also can be in the form of syrups and elixirs, which are typically formulated with sweetening agents such as, for example, glycerol, sorbitol or sucrose. Such formulations also can contain a demulcent, a preservative and flavoring and coloring agents.

The pharmaceutical compositions can be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleagenous suspension. Suitable suspensions for parenteral administration can be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. Formulations suitable for parenteral administration include, for example, aqueous and non-aqueous, isotonic sterile injection solutions, which can contain anti-oxidants, buffers, bacteriostates, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and pres rvativ s. The sterile injectable preparation can be solution or a susp nsion in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution ...ater or 1,3-butanediol. Among the acceptable vehicles a

solvents that can be employed, for example, are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil can be employed including synthetic mono- or diglycerides. In addition, fatty acids such as, for example, oleic acid find use in the preparation of injectables.

The compounds of the present invention also can be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such materials include, for example, cocoa butter and polyethylene glycols. Formulations suitable for vaginal administration can be presented as pessaries, tampons, creams, gels, pastes, and foams.

Formulations suitable for topical administration may be presented as creams, gels, pastes, or foams, containing, in addition to the active ingredient, such carriers as are known in the art to be appropriate.

The multidrug-resistant retroviral protease inhibitors of the present invention, alone or in combination with other suitable components, can be made into aerosol formulations to be administered via inhalation. These aerosol formulations can be placed into pressurized acceptable propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like. They also can be formulated as pharmaceuticals for non-pressured preparations such as in a nebulizer or an atomizer.

The formulations can be presented in unit-dose or multi-dose sealed containers, such as ampules and vials, and can be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid excipient, for example, water, for injections, immediately prior to use. Extemporaneous injection solutions and suspensions can be prepared from sterile powders, granules, and tablets of the kind previously described.

Any suitable dosage level can be employed in the pharmaceutical compositions of the present invention. The dose administered to an animal, particularly a human, in the context of the present invention should be sufficient to effect a prophylactic or therapeutic response in the animal over a reasonable time frame. The amount of active ingredient that can be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. The size of the dose also will be determined by the existence, nature, and extent of any adverse side-effects that might accompany the administration of a particular composition. Suitable doses and dosage regimens can be determined by comparisons to antiretroviral chemotherapeutic agents that are known to inhibit the proliferation of a retrovirus in an infected individual. The preferred dosage is the amount which results in inhibition of retroviral proliferation, particularly the proliferation of multidrug-resistant retroviral HIV, without significant side effects. In proper doses and with suitable administration of certain compounds, the present invention provides for a wide range of antiretroviral chemotherapeutic compositions.

The multidrug-resistant retroviral protease inhibitors of the present invention also can be administered in

combination with other antiretroviral compounds such as, for example, ritonavir, amprenavir, saquinavir, indinavir, AZT, ddI, ddC, D4T, lamivudine, 3TC, and the like, as well as admixtures and combinations thereof, in a pharmaceutically acceptable carrier. The individual daily dosages for these combinations can range from about one-fifth of the minimally recommended clinical dosages to the maximum recommended levels for the entities when they are given singly.

The present invention also provides a method of inhibiting the protease of a multidrug-resistant retrovirus in a mammal infected with a protease-producing, multidrug-resistant retrovirus, which method comprises administering to the mammal a multidrug-resistant, retroviral protease-inhibiting effective amount of a compound of the present invention, so as to inhibit the proliferation of the retrovirus in the mammal. More generally, the present invention provides a method of treating a retroviral, particularly an HIV, infection and, more particularly, a multidrug-resistant HIV infection, in a mammal, particularly a human, wherein a protease-inhibiting effective amount of one or more of the present inventive compounds, alone or in combination with one or more other antiretroviral therapies or compounds, such as AZT, ddI, ddC, D4T, lamivudine or 3TC, is administered to a mammal infected with a retrovirus, particularly HIV, and more particularly multidrug-resistant HIV, the proliferation of which is inhibited by a retroviral protease-inhibiting effective amount of a present inventive compound.

The dose administered to an animal, particularly a human in the context of the present invention should be sufficient to effect a therapeutic response in the animal over a reasonable time frame. The dose will be determined

by the strength of the particular composition employed and the condition of the animal, as well as the body weight of the animal to be treated. The size of the dose will also be determined by the existence, nature, and extent of any adverse side-effects that might accompany the administration of a particular compound. Other factors which effect the specific dosage include, for example, bioavailability, metabolic profile, and the pharmacodynamics associated with the particular compound to be administered in a particular patient. One skilled in the art will recognize that the specific dosage level for any particular patient will depend upon a variety of factors including, for example, the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, CD4 count, the potency of the active compound with respect to the particular retroviral strain to be inhibited, and the severity of the symptoms presented prior to or during the course of therapy. What constitutes a retroviral protease-inhibiting amount, more particularly a HIV protease-inhibiting amount, and more particularly a multidrug-resistant HIV protease-inhibiting amount, of one or more compounds of the present invention, alone or in combination with one or more other currently available antiretroviral compounds can be determined, in part, by use of one or more of the assays described herein. Similarly, whether or not a given retrovirus is inhibited by a retroviral protease-inhibiting amount of a compound of the present invention can be determined through the use of one or more of the assays described herein or in the scientific literature or as known to one of ordinary skill in the art.

One skilled in the art will appreciate that suitable methods of administering the compounds and pharmaceutical compositions of the present invention to an animal are available, and, although more than one route can be used to administer a particular composition, a particular route can provide a more immediate and more effective reaction than another route. One or more of the present inventive compounds, alone or in combination with one or more other antiretroviral therapies or compounds, can be administered to a mammal, in particular a human, as a prophylactic method to prevent retroviral, particularly multidrug-resistant retroviral, such as multidrug-resistant HIV, infection.

Generally, the present method of inhibiting the retroviral protease of a multidrug-resistant retrovirus in a mammal comprises administering to the mammal a multidrug-resistant, retroviral protease-inhibiting effective amount of at least one compound of Formula (I) as disclosed herein. In a preferred embodiment, the present method of inhibiting the retroviral protease of a multidrug-resistant retrovirus in a mammal comprises administering to the mammal a multidrug-resistant, retroviral protease-inhibiting effective amount of at least one compound of Formula (IA) or Formula (IB), or a pharmaceutically acceptable salt, prodrug, or ester thereof. In a further preferred embodiment, the present method of inhibiting the retroviral protease of a multidrug-resistant retrovirus in a mammal comprises administering to the mammal a multidrug-resistant, retroviral protease-inhibiting effective amount of at least one compound of Formula (IC) or Formula (ID), or a pharmaceutically acceptable salt, prodrug, or ester thereof. In a highly preferred embodiment, the present method of inhibiting the retroviral protease of a

multidrug-resistant retrovirus in a mammal comprises administering to the mammal a multidrug-resistant, retroviral protease-inhibiting effective amount of at least one compound of Formula (IE), or a pharmaceutically acceptable salt, prodrug, or ester thereof.

Numerous compounds have been identified that exhibit potent antiretroviral activity, in particular retroviral protease activity, against wild-type HIV. However, among the numerous known potent inhibitors of wild-type HIV and wild-type HIV protease, there are few compounds that have appreciable inhibitory activity against mutant HIV. Indeed, even the most potent wild-type HIV protease inhibitors exhibit little, if any, activity against any one particular mutant strain of HIV. Typically, if a wild-type HIV protease inhibitor exhibits antiretroviral activity against a mutant strain of HIV, the antiviral activity is extremely limited with respect to the mutant strains, and is active with respect to only one or a few particular mutant HIV retroviruses.

Surprisingly, it has been discovered that compound 32 (shown in Figure 3A), which is a potent wild-type HIV inhibitor, possesses remarkably potent and unprecedented broad-spectrum antiviral activity against a wide range of clinically isolated, multiply drug-resistant, human immunodeficiency viruses. The mutant viruses were obtained from infected humans who had received several antiviral drugs. Although applicants do not wish to abound by any one particular theory, it is believed that the combination of the bicyclic ligand (vii) with isostere (vi) gives the antiretroviral compounds of the present invention the unique ability to bind to the active site of the mutant proteases of multiply drug-resistant human immunodeficiency

viruses generally, which trait has heretofore not been reported with respect to any known chemotherapeutic and/or experimental HIV protease inhibitor. A wild-type preliminary screen was utilized to determine the antiretroviral activity of analogs against wild-type HIV. It is predicted that compounds of Formula (I), which have potent antiretroviral or protease-inhibitory activity against wild-type HIV, also will be potent inhibitors of multiple drug-resistant HIV.

The protease inhibitory activity of the compounds of the present invention can be measured by any suitable means. Preferably, protease inhibitory activity is determined by a continuous fluorogenic assay for measuring the anti-HIV protease activity of a protease inhibitor, which method comprises adding a solution of HIV protease to a substrate stock solution, in which the substrate has the formula Ala-Arg-Val-Tyr-Phe(NO_2)-Glu-Ala-Nle-NH_2, to provide a substrate reaction solution. The fluorescence of the substrate reaction solution is then measured at specified time intervals. The solution of HIV protease is then added to a solution of the protease inhibitor and the substrate stock solution, to provide an inhibitor-substrate reaction solution. The fluorescence of the inhibitor-substrate reaction solution is then measured at specified time intervals. The initial velocity of the inhibitor-substrate reaction solution is then calculated by applying the equation:

$V=V_0/2E_t(\{[K_i(1+S/K_m)+I_t-E_t]^2+4K_i(1+S/K_m)E_t\}^{1/2}-[K_i((1+S/K_m)+I_t-E_t])$, wherein V is the initial velocity of the inhibitor reaction solution, V_0 is the initial velocity of the substrate reaction solution, K_m is the Michaelis-Menten constant, S is the substrate concentration, E_t is the

protease concentration, and I_t is the inhibitor concentration.

The continuous fluorogenic assay described herein is highly sensitive and particularly useful for the prediction of the antiviral inhibitory activity of a compound against mutant HIV, more particularly multiple mutant HIV, specifically multidrug-resistant human immunodeficiency viruses. This assay is distinctly advantageous in that it is more sensitive than standard assays in determining the activity of protease inhibitors against multidrug-resistant HIV. The continuous flourogenic assay described herein is disclosed in more detail in Example 13.

To determine the activity of the compounds of the present invention against multidrug resistant HIV, the IC_{50}'s were measured against a panel of clinically isolated mutant HIV isolates. The IC_{50}'s were determined by utilizing the PHA-PBMC exposed to HIV-1 (50 $TCID_{50}$ dose/1X10^6 PBMC) as target cells and using the inhibition of p24 Gag protein production as an endpoint. The assay protocol for determining the multidrug-resistant retroviral inhibitory activity of the compounds of the present invention is disclosed in more detail in Example 14.

The present invention further provides a method of synthesizing the multidrug-resistant, retroviral protease-inhibiting compounds of the present invention. The present synthesis method is generally illustrated in Figure 4, which is a representation of the synthetic approach to preparing a preferred series of the present compounds, wherein a compound of Formula (I) is synthesized in several steps starting from azidoepoxide (i), wherein R^1-R^{17}, m, n, p, Q, W, X, y, and z are defined as above. Referring to Figure 4, amine (ii) is nucleophilically added to azidoepoxide (i),

providing aminoalcohol (iii). The amine functional group of aminoalcohol (iii) is then reacted with intermediate (iv), wherein L represents a leaving group (e.g., halogen, N-oxysuccinimide), which can be displaced by the amine of aminoalcohol (iii), to provide azide (v). Reduction of azide (v), or, when R^5 is not hydrogen, reductive amination with aldehyde $R^5CH=O$, provides intermediate (vi), which is subsequently coupled with activated bicyclic ligand (vii), to provide compounds of Formula I. Of course, it will be appreciated by a person of ordinary skill in the art that there are combinations of substituents, functional groups, R-groups, and the like, which are reactive under particular reaction conditions, and require the utilization of an appropriate protecting group or groups, which are known in the art, to ensure that the desired synthetic transformation will take place without the occurrence of undesired side reactions. For example, possible substituents at R^5 (e.g., NH_2) can be competitive nucleophiles requiring the attachment of an appropriate protecting group thereon (e.g., benzyloxycarbonyl, tert-butoxycarbonyl) in order obtain proper selectivity in the ring opening of epoxide (i) with amine (ii).

Figures 1-3B illustrate the synthesis of a preferred series of compounds of the present invention. Figure 1, which is a synthetic scheme for the synthesis of a particular sulfonamide, illustrates the synthesis of a preferred isosteric core, particularly, the sulfonamide isosteric core represented by aminosulfonamide 15. With reference to Figure 1, aminosulfonamide core 15 can be synthesized by initially providing azidoepoxide 11 and subjecting it to nucleophilic addition with amine 12 to give aminoalcohol 13, which is subsequently converted to

sulfonamide 14 by reaction with 4-methoxybenzenesulfonyl chloride. The azide group of 14 is then reduced to provide aminosulfonamide 15, which can be used as a core for synthesizing numerous multidrug-resistant retroviral protease inhibitors of the present invention.

Figure 2, which is a reaction scheme detailing the preparation of bicyclic alcohols, illustrates the synthesis of a preferred series of bicyclic ligands, particularly bis-tetrahydrofurans 25 and 26. With reference to Figure 2, dihydrofuran 21 is treated with N-iodosuccinimide in the presence of propargyl alcohol to give iodoether 22, which is cyclized to methylene-substituted bis-tetrahydrofuran 23. Ozonolysis of the exo-methylene residue of 23, followed by reduction, provides bicyclic racemic alcohol 24, which is resolved to give, separately, bicyclic alcohol 25 and its enantiomeric acetate ester 26, which ester group of 26 is subsequently hydrolyzed to afford enantiomer 27.

Figures 3A and 3B, which are reaction schemes describing the preparation of two protease inhibitors, illustrate the preparation of two preferred multidrug-resistant HIV protease inhibitors of the present invention. With reference to Figure 3A, compound 32 was synthesized by coupling succinimidocarbonate 31 with aminosulfonamide 15. Succinimidocarbonate 31 was prepared by reacting optically pure bicyclic alcohol 25 with disuccinimidyl carbonate in the presence of triethylamine. Inhibitor 34, which possesses the enantiomeric bis-tetrahydrofuranyl ligand (relative to inhibitor 32), was prepared in the same fashion, except that the enantiomeric bicyclic alcohol 27 was used instead of alcohol 25, as illustrated in Figure 3B.

The following examples further illustrate the present invention but, of course, should not be construed as in any way limiting its scope.

Example 1

This example describes the synthesis of exemplary epoxide 11 (Figure 1), which is used as an intermediate in the synthesis of a particular series of compounds within the scope of the present invention.

Anhydrous CuCN (4.86 g, 54 mmol) was added to a solution of butadiene monooxide (38 g, 540 mmol) in anhydrous tetrahydrofuran (1.2 L) and the resulting mixture was stirred at -78°C. Commercial phenyl magnesium bromide solution (Aldrich) in ether (65 mmol) was added dropwise over a period of 10 min. The resulting reaction mixture was then allowed to warm to 0 °C and it was continued to stir until the reaction mixture was homogeneous. After this period, the reaction mixture was cooled to -78 °C and 0.58 mole of phenylmagnesium bromide solution in ether was added dropwise for 30 min. The reaction mixture was allowed to warm to 23 °C for 1 h. The reaction was quenched by slow addition of saturated aqueous NH_4Cl (120 mL) followed by NH_4OH (70 mL), saturated NH_4Cl (500 ML) and then H_2O (300 mL). The aqueous layer was thoroughly extracted with ethyl acetate (2 x 300 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was distilled under vacuum (0.12 torr) at 95 °C to give *trans*-4-phenyl-2-butene-1-ol (75.6 g).

To a suspension of powdered 4Å molecular sieves (6.6 g) in anhydrous methylene chloride (750 mL), titanium tetraisopropoxide (Aldrich, 3.2 mL) and then diethyl D-

tartrate (2.3 mL) were added. The resulting mixture was cooled to -22 °C and tert-butylhydroperoxide solution in isooctane (Aldrich, 430 mmol) was added over a period of 10 min. The mixture was stirred an additional 30 min and then a solution of *trans*-4-phenyl-2-butene-1-ol (32.6 g, 213 mmol), in anhydrous methylene chloride (120 mL), was added dropwise over a period of 40 min at -22 °C. The reaction mixture was then aged in a freezer at -22 °C for 24 h. After this period, water (100 mL) was added to the reaction mixture at -22 °C and the mixture was allowed to warm to 0 °C. After stirring at 0 °C for 45 min, 20% NaOH in brine (20 mL) was added. The resulting mixture was then allowed to warm to 23 °C and was stirred at that temperature for 1 h. After this period, the layers were separated and the aqueous layer was extracted with methylene chloride (2 x 200 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was diluted with toluene (800 mL) and then evaporated under reduced pressure. The residue was chromatographed over silica gel (35% ethyl acetate in hexane as eluent) to provide (2R, 3R)-epoxy-4-phenylbutan-1-ol (21.8 g).

To a solution of titanium ispropoxide (12 mL) in anhydrous benzene (250 mL) was added azidotrimethylsilane (11 mL) and the resulting mixture was refluxed for 6 h. A solution of (2R,3R)-epoxy-4-phenylbutan-1-ol (5.32 g) in anhydrous benzene (25 mL) was added to the above refluxing mixture. The resulting mixture was refluxed for addition 25 min. After this period, the reaction mixture was cooled to 23 °C and the reaction was quenched with aqueous 5% H_2SO_4 (400 mL). The resulting mixture was stirred for 1 h and the layers were separated and the aqueous layer was

extracted with ethyl acetate (2 x 300 mL). The combined organic layers were washed with saturated $NaHCO_3$ (200 mL), dried over Na_2SO_4 and concentrated under reduced pressure to afford the (2S,3S)-2-hydroxy-3-azido-4-phenyl-butan-12-ol (5.1 g) as a white solid (mp 81-82 °C).

To a stirred solution of the azidodiol (5.1 g) in chloroform (100 mL) at 23 °C, 2-acetoxyisobutyryl chloride (Aldrich, 5mL) was added. The resulting reaction mixture was stirred at 23 °C for 8 h. The reaction was quenched by addition of saturated sodium bicarbonate (100 mL) and the resulting mixture was stirred 30 min. The layers were separated and the aqueous layer was extracted with chloroform (2 x 200 mL). The combined organic layer was extracted with chloroform (2 x 200 mL). The combined organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. The resulting residue was dissolved in anhydrous THF (50 mL) and solid NaOMe (2.1 g) was added. The mixture was stirred for 4 h at 23 °C and after this period, the reaction was quenched with saturated NH_4Cl (50 mL). The resulting mixture was extracted with ethyl acetate (2 x 200 ML). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a residue, which was chromatographed over silica gel (10% ethyl acetate in hexanes) to afford the 3(S)-azido-(1,2R)-epoxy-4-phenylbutane 11 (3.3 g) as an oil: ^1H NMR (300 MHz): $CDCl_3$; δ 7.4-7.2 (m, 5H,), 3.6 (m, 1H), 3.1 (m, 1H), 2.95 (dd, 1H, J = 4.6, 13.9 Hz), 2.8 (m, 3H).

Example 2

This example illustrates the synthesis of azidoalcohol 13 (Figure 1), which can be used as an intermediate in the

synthesis of a preferred series of the compounds of the present ivention.

To a stirred solution of above azidoepoxide 11 (700 mg, 3.7 mmol) in ispropanol (70 mL) was added isobutyl amine (Aldrich, 0.74 mL 7.4 mmol) and the resulting mixture was heated at 80 °C for 12 h. After this period, the reaction mixture was concentrated under reduced pressure and the residue was chromatographed over silica gel to provide azidoalcohol 13 (800 mg) as an oil.

Example 3

This example illustrates the synthesis of azidosulfonamide 14, the structure of which is shown in Figure 1.

To a stirred solution of 13 (600 mg, 2.28 mmol) in CH_2Cl_2 (20 mL) was added 4-methoxybenzenesulfonyl chloride (Aldrich, 530 mg, 2.52 mmol) and saturated aqueous $NaHCO_3$ (6 mL). The resulting heterogeneous mixture was stirred at 23 °C for 12 h. The reaction was diluted with CH_2Cl_2 and the layers were separated. The organic layer was washed with brine, dried over anhydrous magnesium sulfate and concentrated to dryness. The residue was chromatographed over silica gel (25% ethyl acetate/hexane) to provide 900 mg of azidosulfonamide 14.

Example 4

This example illustrates the preparation of aminosulfonamide 15 via reduction of azidosulfonamide 14, as shown in Figure 1.

A solution of 14 (1.53 g) in THF (45 mL), MeOH (10 mL) and acetic acid (0.5 mL), was shaken with 10% palladium on carbon catalyst (200 mg) at 50 psi hydrogen pressure for 2 h. Removal of the catalyst by filtration over celite and concentration under reduced pressure gave a crude residue, which was diluted with CH_2Cl_2 (100 mL), and was washed successively with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried over $MgSO_4$ and concentrated to give the corresponding aminosulfonamide 15 (1.2 g).

Example 5

This example demonstrates the synthesis of trans-2-(propargyloxy)-3-iodotetrahydrofuran 22 (Figure 2).

To a stirred, ice-cold suspension of 15 g (66.6 mmol) of N-iodosuccinimide in 150 mL of CH_2Cl_2 was added a mixture of dihydrofuran 21 (66.6 mmol, 4.67 g, 5.1 mL) and propargyl alcohol (100 mmol, 5.0 g, 5.2 mL) of in 50 mL of CH_2Cl_2 over 20 min. After warming to 24 °C with stirring over 2 h, 200 mL of water were added and the stirring continued for 1 h. The layers were separated and the aqueous layer was extracted with 2 x 100 mL of CH_2Cl_2. The combined organic extracts were washed with brine solution containing small amount of $Na_2S_2O_3$ (70 mg), dried over anhydrous Na_2SO_4, filtered, and concentrated. Chromatography over silica gel using 30% ethyl acetate in hexane afforded (15.4 g, 92%) the title iodoether 22 as an oil.

Example 6

This example illustrates the synthesis of (±)-(3aR, 6aS) and (3aS, 6aR)-3-methylene-4H-hexahydrofuro-[2,3-b]furan 23, as shown in Figure 2.

To a refluxing solution of (20.7 mL, 77 mmol) tributyltin hydride containing AIBN (100 mg) in toluene (200 mL) was added dropwise a solution of 15.4 g (61 mmol) of iodotetrahydrofuran 22 in toluene (50 mL) over a period of 1 h. The resulting mixture was stirred at reflux for an additional 4 h (monitored by TLC). The mixture was then cooled to 23 °C and concentrated under reduced pressure. The residue was partitioned between petroleum ether and acetonitrile (200 mL of each) and the acetonitrile (lower) layer was concentrated. The residue was purified by chromatography on silica gel, using 10% ethyl acetate in hexane as the eluent to provide the title product 23 (5.84 g, 76%) as an oil.

Example 7

This example demonstrates the synthesis of (±)-(3SR, 3aRS, 6aS) and (3R, 3aS, 6aR)-3-hydroxy-4H-hexahydrofuro[2,3-b]furan 24, as shown in Figure 2.

A stream of ozone was dispersed into a solution of 15 (5.84 g, 46.4 mmol) at -78 °C in 150 mL of methanol and 150 mL of $CH_2Cl_2$for 30 min. The resulting blue solution was purged with nitrogen until colorless, then quenched with 20 mL of dimethyl sulfide and the resulting mixture was allowed to warm to 23 °C. The mixture was concentrated under reduced pressure to afford the crude ketone. The resulting crude ketone was dissolved in ethanol (50 mL) and the solution was cooled to 0 °C and sodium borohydride (2.1 g, 55.6 mmol) was added. The reaction mixture was stirred for an additional 2 h at 0 °C and then quenched with 10%

aqueous citric acid (10 mL). The resulting mixture was concentrated under reduced pressure and the reside was partitioned between ethyl acetate and brine. The layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were dried over anhydrous-Na_2SO_4 and concentrated carefully under reduced pressure. The resulting residue was chromatographed over silica gel using 30% ethyl acetate in hexane as the eluent to furnish (4.52 g, 75%) the title racemic alcohol 24 as an oil.

Example 8

This example illustrates the preparation of immobilized Amano Lipase 30, which was used to resolve racemic aminoalcohol 24 (Figure 2).

Commercially available 4 g of Celite® 521 (Aldrich) was loaded on a buchner funnel and washed successively with 50 mL of deionized water and 50 mL of 0.05 N phosphate buffer (pH = 7.0; Fisher Scientific). The washed celite was then added to a suspension of 1 g of Amano lipase 30 in 20 mL of 0.05 N phosphate buffer. The resulting slurry was spread on a glass dish and allowed to dry in the air at 23 °C for 48 h (weight 5.4 g; water content about 2% by Fisher method).

Example 9

This example demonstrates the synthesis of (3R,3aS, 6aR) 3-hydroxyhexahydrofuro[2,3-b]furan 25 by immobilized lipase catalyzed acylation, as illustrated in Figure 2.

To a stirred solution of racemic alcohol 24 (2 g, 15.4 mmol) and acetic anhydride (4 g, 42.4 mmol) in 100 mL of DME was added 2.7 g (about 25% by weight of lipase PS30) of

immobilized Amano lipase and the resulting suspension was stirred at 23 °C. The reaction was monitored by TLC and ^{1}H NMR analysis until 50% conversion was reached. The reaction mixture was filtered and the filter cake was washed repeatedly with ehtyl acetate. The combined filtrate was carefully concentrated in a rotary evaporator, keeping the bath temperature below 15 °C. The residue was chromatographed over silica gel to provide 843 mg (42%) of 25 (95% ee; $a_D^{23°}$ -11.9°, MeOH); ^{1}H-NMR ($CDCl_3$) d 1.85 (m, 2H), 2.3 (m, 1H), 2.9 (m, 1H), 3.65 (dd, J=7.0, 9.1, 1H), 3.85-4.0(m, 3H), 4.45 (dd, J=6.8, 14.6, 1H), 5.7 (d, J=5.1, 1H); also, 1.21 g of 26 after washing with 5% aqueous sodium carbonate (45%, $a_D^{23°}$ +31.8°, MeOH); ^{1}H-NMR ($CDCl_3$)d 1.85-2.1 (m, 2H), 2.1 (s, 3H), 3.1 (m, 1H), 3.75(dd, J=6.6, 9.2, 1H), 3.8-4.1 (m, 3H), 5.2 (dd, J=6.4, 14.5, 1H), 5.7 (d, J=5.2, 1H). Acetate 26 was dissolved in THF (5mL) and 1 M aqueous LiOH solution (20 mL) was added to it. The resulting mixture was stirred at 23°C for 3 h and the reaction was extracted with chloroform (3 x 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The residue was chromatographed over silica gel to provide 733 mg of 27 (97% ee; $\alpha_D^{23°}$ -12.5°, MeOH).

Example 10

This example demonstrates the synthesis of activated carbonates 31 and 33, as illustrated in Figures 3A and 3B.

To a stirred solution of [3R,3aS, 6aS]-3-hydroxyhexahydrofuro[2,3-b]furan 25 (65 mg, 0.5 mmol) in dry CH_3CN (5 mL) at 23°C were added disuccinimidyl carbonate (192 mg, 0.75 mmol) and triethylamine (0.25 mL). The resulting mixture was stirred at 23°C for 12 h. The

reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and the mixture was concentrated under reduced pressure. The residue was extracted with CH_2Cl_2 (2 x 25 mL) and the combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure gave a residue, which was chromatographed over silica gel (50% ethyl acetate/hexane) to furnish (3R, 3aS, 6aR) 3-hydroxyhexahydrofuro[2,3-b]furanyl-succinimidyl carbonate 31 (70 mg) as a brown oil. Carbonate 33 (65 mg) was prepared from 60 mg of alcohol 27 by following a similar procedure.

Example 11

This example illustrates the preparation of multidrug-resistant HIV inhibitor 32, as illustrated in Figure 3A.

To a stirred solution of amine 15 (82 mg, 0.2 mmol) in dry CH_2Cl_2 (5 mL) was added succinimidyl carbonate 31 (55 mg, 0.18 mmol). The resulting solution was stirred at 23°C for 12 h. After this period, the reaction was quenched with saturated aqueous $NaHCO_3$ (10 mL) and diluted with CH_2Cl_2 (25 mL). The layers were separated and the organic layer was washed with brine (15 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent under reduced pressure afforded a residue, which was purified by silica gel chromatography (75% ethyl acetate/hexane) to furnish compound 32 (85 mg) as a white solid (m.p 55-58°C). ^{1}H-NMR ($CDCl_3$, 400 MHz); δ 7.71(d, 2H, J=8.8 Hz), 7.29-7.20 (m, 5H), 6.99 (d,2H,J=7.0 Hz), 5.65 (d,1H,J=5.19), 5.01 (m, 2H), 3.95-3.82 (m, 7H), 3.69 (m,2H), 3.0-2.7 (m, 6H), 1.85 (m, 1H), 1.64-1.45 (m, 3H), 0.90 (two d, 6H, J=6.5Hz, 6.6 Hz).

Example 12

This example illustrates the preparation of multidrug-resistant HIV inhibitor 33, as illustrated in Figure 3B.

Carbonate 33 (55 mg) was reacted with amine 15 (82 mg, 0.2 mmol) according to the procedure mentioned above to provide compound 34 (81 mg). ^{1}H-NMR ($CDCl_3$, 300 MHz); δ 7.69(d, 2H, J=8.8 Hz), 7.28-7.21 (m,5H), 6.87 (d,2H,J=5.84 Hz), 5.67 (d,1H,J=5.46 Hz), 5.0 (m, 2H), 3.86-3.81 (m, 7H), 3.58 (dd, 2H, J=6.6 Hz, 3.6 Hz, 3.17-2.73 (m, 6H), 2.17-1.83 (m, 4H), 0.90 (two d, 6H, J=6.5Hz, 6.6 Hz).

Example 13

This example describes the protocol for the sensitive continuous fluorogenic assay for HIV protease described above and its application. Using this assay, the inhibitory activity of compound 32 (Fig. 3A) was tested against the proteases of wild-type HIV-1 (WT) and various mutant strains: D30N, V32I, I84V, V32I/I84V, M46F/V82A, G48V/L90M, V82F/I84V, V82T/I84V, V32I/K45I/F53L/A71V/I84V/L89M, V32I/L33F/K45I/F53L/A71V/I84V, and 20R/36I/54V/71V/82T, which protease enzymes are available from Dr. John W. Erickson, Structural Biochemistry Program, SAIC, Frederick, P.O. Box B, Federick, MD 21702-1201, upon written request. The inhibition constant for wild-type HIV-1 , K_{imut}/K_{iwt} ratio, and the vitality was measured. (*See* Gulnik et al., *Biochemistry*, *34*, 9282-9287 (1995). Protease activity was measured using the fluorgenic substrate Lys-Ala-Arg-Val-Tyr-Phe(NO_2)-Glu-Ala-Nle-NH_2 (Bachem Bioscience, Inc.). (*See* Peranteau et al., D.H. (1995) *Anal. Biochem.*).

Typically, 490 µl of 0.125 M ACES-NaOH buffer, pH 6.2, containing 1.25 M $(NH_4)_2SO_4$, 6.25 mM DTT and 0.1% PEG-8000

was mixed with 5 µl of titrated protease (final concentration 1-5 nM) and incubated 3 min at 37 °C. The reaction was initiated by the addition of 5 µl of substrate stock solution in water. Increase in fluorescence intensity at the emission maximum of 306 nm (excitation wavelength was 277 nm) was monitored as a function of time using Aminco Bowman-2 luminescence spectrometer (SLM Instruments, Inc.). The initial rate of hydrolysis was calculated by second degree polynomial fit using SLM AB2 2.0 operating software. Kinetic parameters were determined by nonlinear regression-fitting of initial rate versus substrate concentration data to the Michaelis-Menten equation using program Enzfiter version 1.05.

For inhibition studies, inhibitors were prepared as stock solutions at different concentrations in dimethylsulfoxide. In a typical experiment 485 µl of 0.125 M ACES-NaOH buffer, pH 6.2, containing 1.25 M $(NH_4)_2SO_4$, 6.25 mM DTT AND 0.1% PEG-8000, was mixed with 5 µl of inhibitor stock solution and 5 µl of titrated protease (final concentration of 1-5 nM) and preincubated 3 min at 37 °C. The reaction was initiated by the addition of 5 µl of substrate stock solution in water. For data analysis, the mathematical model for tight-binding inhibitors was used. (*See* Williams and Morrison (1979), In: Methods of Enzymol. 63, (ed. D.L. Purich), 437-467, Academic Press, NY, London). The data were fitted by nonlinear regression analysis to the equation: $V=V_0/2E_t(\{[K_i(1+S/K_m)+I_t-E_t]^2+4K_i(1+S/K_m)E_t\}^{1/2}-[K_i((1+S/K_m)+I_t-E_t])$ with the program Enzfiter (version 1.05), where V and V_0 are initial velocities with and without inhibitor, respectively, K_m is a Michaelis-Menten constant, and S, E_t and I_t are the

concentrations of substrate, active enzyme, and inhibitor, respectively. The results are shown below in Table 1.

Table 1

Enzyme	K_i (pM)	$K_{i\ wt}/K_{i\ mnt}$
WT	14	1
D30N	<5	0.33
V32I	8	0.57
I84V	40	2.85
V32I/I84V	70	5
M46F/V82A	<5	0.33
G48V/L90M	<5	0.33
V82F/I84V	7	0.5
V82T/I84V	22	1.57
V32I/K45I/F53L/A71V/I84V/L89M	31	2.2
V32I/L33F/K45I/F53L/A71V/I84V	46	3.3
20R/36I/54V/71V/82T	31	2.2

The above results demonstrate that compound 32 is a potent inhibitor of multidrug-resistant HIV protease. These data provide strong evidence of the potent and broad-spectrum multidrug-resistant antiretroviral activity of compound 32.

Example 14

This example illustrates the potent and broad-spectrum multidrug-resistant antiretroviral activity of an exemplary compound of the present invention.

Compound 32, shown in Figure 3A, was tested side-by-side with four other known HIV-1 protease inhibitors against various wild-type HIV-1 strains (HIV-$1_{ERS104pre}$, HIV-1_{LAI}, and HIV-1_{BAL}), and mutant multidrug-resistant HIV-1 strains clinically isolated from patients receiving several antiviral drugs. The mutant multidrug-resistant HIV-1 strains, numbered 1-8, are based on the profile of the patients from which the mutant viruses were isolated. The patients from which the mutant strains were isolated had a

history of anti-HIV therapy with a variety of different drugs such as, for example, ritonavir, saquinavir, indinavir, amprenavir, AZT, ddI, ddC, d4T, 3TC, ABV (abacavir), DLV (delaviridine), and PFA (foscarnet). The patient profiles are shown below in Table 2.

Table 2

Patient/ Isolate Code	CD4$^+$ (/mm^3)	HIV-1 RNA level (copies/mL)	Months on Antiviral Therapy	Prior and Present Anti-HIV Therapy
1	361	246,700	64	AZT, ddI, ddC, d4T, 3TC, ABV, IDV, RTV, SQV, AMV, DLV
2	3	553,700	46	AZT, ddI, ddC, d4T, 3TC, ABV, IDV, SQV, AMV
3	108	42,610	39	AZT, ddI, ddC, d4T, 3TC, ABV, IDV, SQV, AMV
4	560	60,000	81	AZT, ddI, ddC, U90, d4T, 3TC, ABV, IDV, SQV, AMV
5	-	-	32	AZT, ddI, ddC, d4T, 3TC, ABV, IDV, SQV, AMV
6	-	-	34	AZT, ddI, ddC, d4T, 3TC, ABV, IDV, SQV, AMV
7	-	-	83	AZT, ddI, ddC, d4T, 3TC, ABV, IDV, SQV, RTV, AMV
8	-	-	69	AZT, ddI, ddC, d4T, 3TC, PFA, ABV, IDV, SQV, AMV

The four known chemotherapeutic HIV protease inhibitors used for comparative purposes in this example have been utilized in actual human HIV chemotherapy, and are: Ritonavir ("RTV," Abbott Laboratories); Indinavir ("IDV," Merck Research Laboratories); Amprenavir (AMV, *See* Ghosh et al., *Bioorg. Med. Chem. Lett.*, 8, 687-690 (1998)); and Saquinavir ("SAQ", Roche Research Centre). The IC_{50} values (μM) for all five compounds were determined with respect to wild-type and multidrug-resistant HIV-1.

The IC_{50}'s were determined by utilizing the PHA-PBMC exposed to HIV-1 (50 $TCID_{50}$ dose/1X10^6 PBMC) as target cells and using the inhibition of p24 Gag protein production as an endpoint. All drug sensitivities were performed in

triplicate. In order to determine whether the HIV isolates were SI or NSI, an aliquot of viral stock supernatant, containing 100 $TCID_{50}$, was cultured with 1 X 10^5 MT-2 cells in a 12-well plate. Cultures were maintained for four weeks and were examined for syncytium formation twice a week. The results are shown below in Table 3.

Table 3

		IC_{50} (μM)				
Pheno-type	Patient/ Isolate code (See Table 2)	RTV	IDV	AMV	SAQ	Compound 32
SI	$HIV\text{-}1_{RF/I84Vpro}$	0.055	0.013	0.021	0.01	<0.001
SI	$HIV\text{-}1_{LAI}$	0.0047	0.019	0.019	0.0054	0.0004
NSI	$HIV\text{-}1_{RAL}$	0.018	0.0056	0.014	0.0037	0.0004
	1	>1	>1	0.29	0.29	0.002
	2	>1	0.24	0.24	0.035	<0.001
	3	>1	0.46	0.33	0.036	<0.001
	4	>1	0.24	0.4	0.033	0.001
NSl	5	>1	0.8	0.28	0.24	0.002
	6	>1	0.37	0.11	0.19	<0.001
	7	>1	>1	0.42	0.12	0.004
	8	>1	>1	0.22	0.009	0.001

The above IC_{50}'s clearly demonstrate the broad-spectrum and extraordinarily potent activity of compound 32 against wild-type HIV-1 and the eight different multidrug-resistant clinical isolates tested. For example, compound 32 exhibits nanomolar and sub-nanomolar potency against all the multidrug-resistant strains tested, whereas Ritonavir, a reasonably potent wild-type inhibitor, is virtually inactive toward the resistant viruses. Moreover, compound 32 is about 9 to about 150 times more potent against the multidrug-resistant viruses than Saquinavir, one of the most potent known compounds against known multidrug-resistant strains of HIV-1. Patients with viral plasma loads greater than 10,000 RNA copies/mm^3 are at risk for developing fatal AIDS complications. There are no effective therapeutic

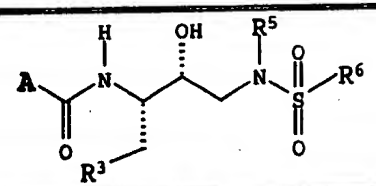
options currently available for these patients infected with these multidrug resistant viruses. Compound 32, and analogs thereof, are predicted to be potent inhibitors of these viral strains in vivo.

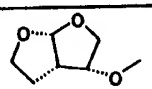
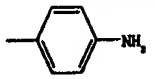
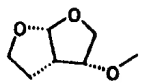
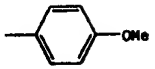
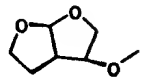
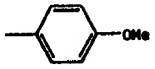
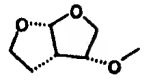
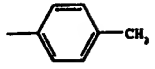
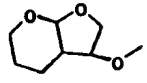
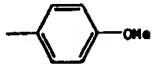
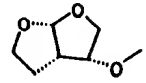
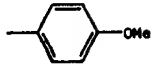
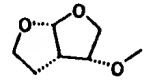
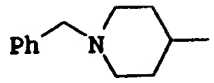
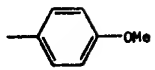
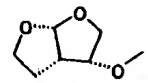
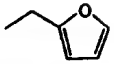
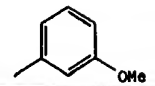
Example 15

This example demonstrates the wild-type antiretroviral activity of the compounds of the present invention.

It is predicted that the activity of the present inventive compounds against wild-type HIV protease correlates with of antiretroviral activity against multidrug-resistant HIV. Numerous compounds of the present invention were tested against wild-type HIV (*See*, Ghosh et al., *J. Bioorg. Med. Chem. Lett., 8,* 6870690 (1998)). Exemplary compounds, which demonstrate potent wild-type HIV protease activity, are shown below in Table 4.

Table 4



A	R^3	R^5	R^6	Ki (nM)	ID_{50} (nM)	Comments
	Ph			2.1	4.5	
	Ph			1.1	1.4	Compound 32 (Fig. 3A)
	Ph					Compound 34 (Fig. 3B)
	Ph			1.2	3.5	
	Ph			2.2	4.5	
	Ph					
						
	Ph					

Example 16

This example demonstrates the oral absorption of compound 32 in an *in vivo* experimental model.

Compound 32 was orally administered to a rat at a dose of about 40 mg per kg body mass, using a PEG 300 vehicle as a carrier. The plasma blood levels of compound 32 were measured over a 24 h period after oral administration. The results are shown in Table 5 below.

Table 5

Time After Administration		Plasma Concentration	
Hours	Minutes	(nM)	(ng/mL)
0.28	17	1598	898
1.00	60	878	493
2.07	124	626	352
4.01	240	670	377
6.01	360	594	334
8.05	483	1115	627
12.04	722	246	138
14.08	845	102	57
24.00	1440	82	46

These results demonstrate that compound 32 maintains high blood levels (e.g., nearly 0.6 uM after 6 hours) long after oral administration. Although applicants do not wish to abound by any one particular theory, it is believed that the non-peptide structure of the compounds of the present invention make them less prone to biological (e.g., enzymatic) degradation, and thereby contribute to their prolonged blood levels after oral administration. From these data, the compounds of the present invention are predicted to have excellent oral bioavailability in humans, and maintain therapeutically significant blood levels over prolonged periods after oral administration.

Example 17

This example demonstrates the influence of human protein binding on the antiviral activity of compound 32. Several potent and orally bioavailable HIV protease inhibitors failed to have in vivo antiviral efficacy. These failures have been ascribed, but not definitively proven, to be due to excessive binding to human plasma proteins, particularly serum albumin and AAG. The protein binding against human alpha acid glycoprotein (AAG, 10 μM) and against human serum albumin (HAS, 300 μM) were compared for compound 32 and amprenavir, a structurally related analog that is an FDA approved drug. The results are shown in Table 6.

Table 6

	IC_{50} (μM)		
Compound	(-)	AAG	Alb
32	0.0015(1X)	0.0022(1.5X)	0.003(2X)
amprenavir	0.029(1X)	0.18(6X)	0.021(1X)

These data demonstrate that the presence of AAG and HAS in physiologically excessive amounts does not adversely affect the antiviral activity of compound 32. From these data, the affinity of compound 32 for human AAG and HSA is predicted to be actually lower than that for amprenavir, a known drug. From these data, the compounds of the present invention are expected to have excellent in vivo efficacy in humans, and maintain therapeutically significant levels over prolonged periods of time.

Example 18

This example describes the inhibitory activity of compounds 35 (Fig. 5A), 36 (Fig. 5B), 37 (Fig. 5C) and 38 (Fig. 5D). In accordance with the technique disclosed in Example 13 above, the inhibitory activity of these compounds was tested against proteases of the wild-type HIV-1. Compound 36, 37 and 38 were also tested against proteases containing the deleterious drug resistance associated mutations V82F/I84V and G48V/V82A. The results of these experiments are shown below in Table 7.

Table 7

COMPOUND	ENZYME	K_i (pM)	K_i wt/K_i mut
35	WT	81	1
36	WT	5<	
	V82F/I84V	24.4	>4.9
	G48V/V82A	15.3	>3.0
37	WT	12	1
	V82F/I84V	25.7	2.1
	G48V/V82A	64	5.3
38	WT	>5	
	V82F/I84V	66.8	>13
	G84V/V82A	34	> 6.8

These results further demonstrate compounds of the present invention that are potent inhibitors against mutant proteases.

Example 19

This example further demonstrates the broad-spectrum and potent activity of exemplary compounds of the present invention against multidrug-resistant clinical isolates.

The IC_{50} values (μM) for all compounds 32, 35, 36, 37, and 38 were determined with respect to wild type clinical isolates HIV-1_{LAI} and HIV-1_{BaL}. The latter is a monocytotropic strain of HIV.

The IC_{50}'s for isolates HIV-1_{LAI} and HIV-1_{Ba-L} were determined by exposing the PHA-simulated PBMC to HIV-1 (50 $TCID_{50}$ dose/1X10^6 PBMC), in the precence of various concentrations of compounds 32, 35, 36, 37 and 38, and using the inhibition of p24 Gag protein production as an endpoint on day 7 of culture ("p24 assay"). All drug sensitivities were performed in triplicate. The IC_{50}'s for isolate HIV-1_{LAI} were also determined by exposing MT-2 cells (2x10^3) to 100 $TCID_{50}$s of HIV-1_{LAI} cultured in the presence of various concentrations of compounds 32, 35, 36, 37 and 38. The IC_{50}'s were determined using the MTT assay on day 7 of culture. All sensitivities were determined in duplicate. The results are shown below in Table 8.

Table 8

Virus	Cell Type /Assay	Comp. 32 IC_{50} (μM)	Comp. 35 IC_{50} (μM)	Comp. 36 IC_{50} (μM)	Comp. 37 IC_{50} (μM)	Comp. 38 IC_{50} (μM)
HIV-1_{LAI}	MT-2/MTT	0.00022	0.028	0.017	0.0053	0.028
HIV-1_{LAI}	PBMC/p24	0.00022	0.020	0.034	0.0027	0.0080
HIV-1_{Ba-L}	PBMC/p24	0.00033	0.013	0.038	0.0030	0.0093

These results demonstrate the potent antiretroviral activity of particular compounds of the present invention.

Example 20

This example further illustrates the potent and broad-spectrum multidrug-resistant antiretroviral activity of an exemplary compound of the present invention.

Compound 32, shown in Figure 3A, was tested against various mutant multidrug-resistant HIV-1 strains clinically isolated from patients. These isolates were all taken from patients who failed therapy on one or more HIV protease inhibitors due to high level clinical resistance. All of these isolates exhibit

high level phenotypic resistance in antiviral assays against many of the commonly use HIV protease inhibitor drugs. Compound 32 was tested against these multidrug-resistant clinical isolates side-by-side with known drugs that are commonly used in HIV antiviral therapy, including reverse transcriptase inhibitors such as AZT, 3TC, DDI, DDC, and D4T, and protease inhibitors such as Indinavir (Ind.), Nelfinavir (Nel.), Ritonavir (Rit.), and Saquinavir (Saq.). The IC_{50}'s for compound 32 and the comparative drugs against the multidrug-resistant HIV-1 clinical isolates, and against wild-type HIV-1 (WT), are shown in Table 9a.

The mutant multidrug-resistant HIV-1 strains corresponding to each patient, numbered 9-35, were genetically analyzed in terms of the nucleic acid sequences of the protease (PR) and a portion of the reverse transcriptase (RT) genes from which mutations in these enzymes were determined. The mutations in the protease and reverse transcriptase of the multidrug-resistant viruses isolated from each patient are shown below in Table 9b.

Table 9a

	IC_{50} (μM)									
Patient Isolate	AZT	3TC	DDI	DDC	D4T	Ind.	Nel.	Rit.	Saq.	Comp. 32
9	0.01	0.39	0.7	0.15	0.91	1.087	0.98	0.53	>0.3125	0.0003
10	0.02	1.35	1.7	0.37	1.29	>1.25	>1.25	2.03	>0.3125	0.0017
11	0.11	23.61	2.4	0.18	3.10	0.012	0.03	0.01	0.001	0.0004
12	0.07	0.78	0.9	0.20	1.23	>1.25	>1.25	2.47	>0.3125	0.0010
13	0.17	1.04	0.5	<0.1221	0.78	>1.25	0.47	1.64	>0.3125	0.0004
14	0.64		2.4	<0.1221	1.10	0.089	0.01	0.04	0.040	0.0003
15	0.20	>31.25	2.2	0.32	1.10	0.265	0.47	1.14	>0.3125	0.0011
16	0.97	27.98	3.5	0.57	1.81	0.384	0.86	1.34	>0.3125	0.0031
17	>1.25	28.05		0.63	4.28	0.502	0.52	0.87	0.107	0.0022
18	0.55	>31.25	2.2	0.48	2.08	0.369	0.60	3.02	0.039	0.0019
19	>1.25	>31.25	36.6	6.80	35.63	0.784	0.50	2.94	0.055	0.0005
20	1.25	3.21	7.1	0.57	22.54	0.591	0.58	1.90	0.032	
21	>1.25	1.69	1	0.38	3.28	1.250	>1.25	2.18	0.21	0.0023
22	1.02	>31.25	3.7	0.63	4.68	0.173	0.10	0.56	0.003	
23	0.19	>31.25	1.8	0.28	1.00	0.461	0.28	1.82	0.008	0.0004
24										0.0004
25										0.0019
26										0.0019
27	0.03	1.72	2.6	0.41	4.00	>1.25	>1.25	2.97	>0.3125	0.0009
28	>1.25	2.08	2.8	0.36	5.44	1.040	>1.25	2.66	>0.3125	
29	>1.25	2.24	3.8	0.34	5.29	0.569	0.67	0.36	0.050	0.0009
30	0.16	>31.25	2.8	0.24	2.52	0.270	0.52	1.03	0.191	0.0019
31		>31.25	2.6	<0.1221	3.11	0.251	0.24	0.85	0.074	0.0010
32	0.32	>31.25	8.4	0.91	2.41	0.223	0.22	0.37	>0.3125	
33	0.51	>31.25	2.0	0.28	2.73	0.133	0.35	0.18	0.059	0.0005
34	>1.25	>31.25	9.1	1.13	7.71	0.595	0.26	3.38	0.063	0.0024
35	0.88	>31.25	17.0	2.46	18.13	0.509	0.48	2.60	0.0616	0.0012
(WT)	0.022	0.264	0.895	0.243	1.059	0.02	0.031	0.019	0.007	0.0007

Table 9b

Isolate		Mutations												
9	PR	V003I	L010I	S037N	R041K	G048V	I054S	I062V	L063S	1064L	1064L	A071V	V082A	1093L
	RT	P004S	V0601	V0901	E122K	I135V	Q174K	Y181C	E194E/K	G196E	R211K	L214F	V245M	R227K
		E297R	L301L/I											
	PR	V003I	L010I	S037N	R041K	G048V	I054S	I062V	L063S	1064L	1064L	A071V	V082A	1093L
	RT	P004S	V0601	V0901	E122K	I135V	T165A/T	Q174K	Y181C	E194K	G196E	R211K	L214F	H221H/Y
		V245M	R277K											
11	PR	V003I	L010I	1015V	M036I	S037N	R041K	L063T	I093L					
	RT	K020R/K	M041L	K043Q	E044D	V060I	D067N	T069D	E122E/K	D123E	Y181C/Y	M184V	G196E	H208Y
		L210W	R211K											
12	PR	V003I	L010I	1015V	K020R	M036I	S037N	R041K	G048V	I054T/I	L063T	A071V	T074A	V082A/V
		1093L												
	RT	M041L	K043Q	E044D	V060I	D067N	T069D	L074L/I	K103N	D123E	I135T	Y181C	G196E	H208Y
		L201W	R211K											
13	PR	V0031	L010I	1015V	K020R/K	M036I	S037N	R041K	G048V/G	I054T/I	Q058E/Q	Q061R/Q	L063T	A071A/V
		1072T/I	T074A/T	V082A	I093L									
	RT	M041L	K043Q	E044D	V060I	D067N	T069D	L074L/I	K103N	D123E	I135T/I	Y181C	G196E	H208Y
		L210W	R211K											

(Table 9b con't.)

14	PR	V003I	L010I	K020R	E035D	M036I	S037D	R041K	G048V	L063C	A071V	I072T	V082A/V	I093L
	RT	M041L	T069T/N	L074L/V	E122K	D123E	Y181C	Q207E	L210W	R211K	L214F	T215Y	L228R	E248D
		R277K	E297K											
15	PR	V003I	L010I	E035D	R041K	L063P	A071A/V	I072V/I	G073R/C	V077I	I084V	L090M	I093L	
	RT	D067N	T069D	I142V	E169D	Y181C	M184V	Q207E	R211K	L214F	T215Y	D250E	P272A	Q278E
		L283I	I293V											
16	PR	V003I	L010I	I013V	E035D	S037A	R041K	L063P	A071V	G073S	I084V	L090M		
	RT	K020R	M041L	K043N	D067N	D123N	D177E	I178M/I	M184V	G196E	E203D	L214F	T215Y	K219Q
		R277K	G333E											
17	PR	V003I	L010I	I013V	E035D	S037A	R041K	L063P	A071V	G073G/S	I084V	L090M		
	RT	K020R	M041L	K043N	D067N	D123N	D177E	I178M/I	M184V	G196E	E203D	L214F	T215Y	R277K
		G333E	A360T											
18	PR	V003I	L010V	S037N	K043T	I054V	L063P	A071V	V082A	L090M				
	RT	K020R	V035M	K064H	D067G	T069N	K070R	K102R/K	V111BI	E122K	I135T	S162A	M184V	T215S
		D128E	K219Q											
19	PR	V003I	L010I	L019I	S037Q	M046L	I054V	R057K	L063P	A071V	V082A	L090M		
	RT	K020R	T058N	A062V	S068G	T069T/I	V075I	F077L	A098S	K103N	F116Y	I135T	I142M	Q151M
		Y181C	M184V											

(Table 9B con't.)

20	PR	V003I	L010I	T012P	K014R	I015V/I	G016E	S037N	M046I	I054V	K055R	I062V	L063N	A071T
		V077I	V082A	I085V	L090M									
	RT	K020R	V035I	T039A	M041L	K043E	E044A	D067N	V075A	K103N	V118I	I135M	Y181C	H208Y
		L210W	R211K											
21	PR	V003I	L010I	1015V	K020R	E035D	M036I	S037K	R041N	K043T/K	M041I	L063P	H069K	A071V
		T074S	V082F	N088E	L084M	L090M	I093L							
	RT	K020R	V035T	T039R	M041L	K043E	E044D	V060I	I063M/I	D067N	T069D	A098G	V118I	D121H
		I135T/I	I142V											
22	PR	V003I	L010I	E034E/Q	S037H	M046I	I054V	I062V	L063S	V082A	L089L/M			
	RT	K020R/K	T039A/T	M041L	K043E	E044D	D067N	V118I	M184V	E203E/K	Q207E	H208Y	L210W	R211K
		L214F	T215Y											
23	PR	V003I	L010I	1015V	K020I	L024I	M036I	S037N	I054V	R057K	L063P	A071V	V082A	
	RT	K011R	D067N	K070R	I135T	Y181V/D	M184V	D218E/D	K219Q	P272A	R277K	R284R/K	I293V	E297V
		M357T/M	G359G/S											
24	PR	V003I	I015V	D030N	E035D	S037D	L063P	V077I	N088D					
	RT	K064R	E122K	D123E	D177E	M184V	G196R	R211G	L214F	V245T/M	E297A	I326V	I329L	T338S
		N348I	R358K											
25	PR	V003I	K020I	T026T/I	S037N	M046I	L063P	A071V	G073S	V077I	I084V	L090M	I093L	
	RT	V035M	D067N	T069D	K070R	E122P	D177E	M184V	I202V	Q207E	R211K	L214F	T215F	K219Q
		E224K	R277K											

(Table 9b con't.)

26	PR	V003I	L010I	S037N	R041K	G048V	I054S	I062V	L063S	I064L	A071V	V082A	I093L	
	RT	P004S	V060I	V090I	E122K	I135Y	T135A/T	Q174K	Y181C	E194K	G196E	R211K	L214F	H221H/Y
		V245M	R277K											
27	PR	V003I	L010I	I015V	K020R	M036I	S037N	R041K	G048V	I054T/I	L063T	A071A/V	T074A	V082A
		I093L												
	RT	M041L	K043Q	E044D	V060I	D067N	T069D	L074L/I	K103N	F116F/L	D123E	I135T	Y181C	G196E
		H208Y	L210W											
28	PR	V003I	L010I	I015V	M036I	S037D	G048V	I054V	D060E	Q061E	I062V	I064V	A071V	V082A
		L090M	I093L											
	RT	P004S	M041L	D067N	T069D	K070R	V090I	K103N	I135T	S162A	V179I	Y181C	G196E	Q207E
		L214F	T215F											
29	PR	V003I	L010I	K020I	S037N	M046M/I	L063P	I072I/K	G073C	V077I	L090M			
	RT	V035I	T039A/E	M041L	E044D	L074L/V	R083K	K102Q	S162C	I178L	E203K	H208Y	L210W	R211K
		L214F	T215Y											
30	PR	V003I	L010I	E035D	R041K	L063P	A071A/V	I072V/I	G073G/S	V077I	I084V/I	L090M	I093L	
	RT	D067N	T069D	I142V	E169D	Y181C	M184V	Q207E	R211K	L214F	T215Y	D250E	P272A	Q278E
		L283I	I293V											

(Table 9b con't.)

31	PR	V003I	L010L/I	E035D	M036M/I	S037N	M046X	I054V	L063P	I066F	A071V	V082A/T	I084V/I	
	RT	K032R/K	K064R	D067N	K070R	K103N/K	E122K	Y181F/C	M184V	R211K	L214F	D218E	K219Q	E248D
		T286A	I293V											
32	PR	V003I	L010I	S037N	G048V	I054V	I062V/I	L063P	A071A/T	V077I	V082A	I093L		
	RT	K020R	M041L	D123N	I178L	M184V	T200A/T	E203D	Q207E	L210L/W	L214F	T215Y	R277K	T286A
		Q334L/Q	T338S/T											
33	PR	V003I	L010I	E035D	M036I	S037D	D060E	L063P	I064V	I084V	L090M			
	RT	M041L/M	D067N	T063T/N	K070R	D177D/E	M184V	I202V	Q207E	L210W	R211K	L214F	T215Y	K219Q
		V245T	P272A											
34	PR	V003I	L010V	S037N	K043T	I054V	L063P	A071V	V082A	L090M				
	RT	K020R	V035M	K064H	D067G	T069N	K070R	K102R/K	V1181I	E122K	I135T	S162A	M184V	T215S
		D218E	K219Q											
35	PR	V003I	L010I	L019I	S037Q	M046L	I054V	R057K	L063P	A071V	V082A	L090M		
	RT	K020R	T058N	A062V	S068G	T069T/I	V075I	F077L	A098S	K103N	F116Y	I135T	I142M	Q151M
		Y181C	M184V											

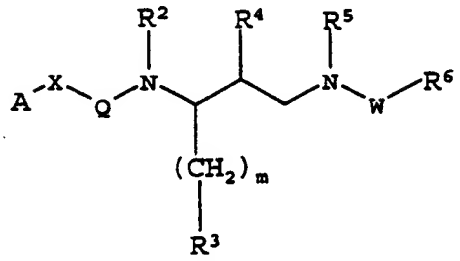
The results of this experiment further show the effectiveness of an exemplary compound of the present invention against a wide range of viral mutants compared to other well-known inhibitors. These mutant viruses represent a panel of the most broadly cross resistant clinical isolates known to date based on their resistance to therapeutically used HIV protease inhibitors. Compound 32 was consistently potent against all of the clinically isolated mutant viruses tested, and was significantly more potent against these multidrug resistant viruses than the comparative drugs which are currently used in human HIV-1 therapy. Compound 32 was ten to one-thousand times more potent against these multidrug resistant viruses than even saquinavir, one of the most potent known compounds against multidrug-resistant HIV-1.

All of the references cited herein, including patents, patent applications, and publications, are hereby incorporated in their entireties by reference.

While this invention has been described with an emphasis upon preferred embodiments, it will be obvious to those of ordinary skill in the art that variations of the preferred embodiments may be used and that it is intended that the invention may be practiced otherwise than as specifically described herein. Accordingly, this invention includes all modifications encompassed within the spirit and scope of the invention as defined by the following claims.

WHAT IS CLAIMED IS:

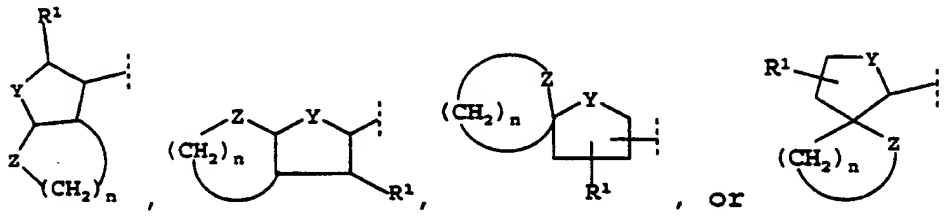
1. A compound represented by the formula:



(I),

or a pharmaceutically acceptable salt, a prodrug, or an ester thereof, wherein:

A is a group of the formula:



;

R^1 is H or an alkyl, an alkenyl, an alkynyl, a cycloalkyl, a cycloalkylalkyl, an aryl, an aralkyl, a heterocycloalkyl, a heterocycloalkylalkyl, a heteroaryl, or a heteroaralkyl, in which at least one hydrogen atom is optionally substituted with a substituent selected from the group consisting of OR^7, SR^7, CN, NO_2, N_3, and a halogen, wherein R^7 is H, an unsubstituted alkyl, an unsubstituted alkenyl, or an unsubstituted alkynyl;

Y and Z are the same or different and are independently selected from the group consisting of CH_2, O, S, SO, SO_2, NR^8, $R^8C(O)N$, $R^8C(S)N$, $R^8OC(O)N$, $R^8OC(S)N$, $R^8SC(O)N$, $R^8R^9NC(O)N$, and $R^8R^9NC(S)N$, wherein R^8 and R^9 are each selected from the group consisting of H, an unsubstituted alkyl, an unsubstituted alkenyl, and an unsubstituted alkynyl;

n is an integer from 1 to 5;

X is a covalent bond, CHR^{10}, $CHR^{10}CH_2$, CH_2CHR^{10}, O, NR^{10}, or S, wherein R^{10} is H, an unsubstituted alkyl, an unsubstituted alkenyl, or an unsubstituted alkynyl;

Q is C(O), C(S), or SO_2;

R^2 is H, a C_1-C_6 alkyl, a C_2-C_6 alkenyl, or a C_2-C_6 alkynyl;

m is an integer from 0 to 6;

R^3 is a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl in which at least one hydrogen atom is optionally substituted with a substituent selected from the group consisting of alkyl, $(CH_2)_pR^{11}$, OR^{12}, SR^{12}, CN, N_3, NO_2, $NR^{12}R^{13}$, $C(O)R^{12}$, $C(S)R^{12}$, CO_2R^{12}, $C(O)SR^{12}$, $C(O)NR^{12}R^{13}$, $C(S)NR^{12}R^{13}$, $NR^{12}C(O)R^{13}$, $NR^{12}C(S)R^{13}$, $NR^{12}CO_2R^{13}$, $NR^{12}C(O)SR^{13}$, and a halogen, wherein:

p is an integer from 0 to 5;

R^{11} is a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl in which at least one hydrogen atom is optionally substituted with a substituent selected from the group consisting of a halogen, OH, OCH_3, NH_2, NO_2, SH, and CN; and

R^{12} and R^{13} are independently selected from the group consisting of H, an unsubstituted alkyl, an unsubstituted alkenyl, and an unsubstituted alkynyl;

R^4 is OH, =O (keto), NH_2, or $NHCH_3$;

R^5 is H, a C_1-C_6 alkyl radical, a C_2-C_6 alkenyl radical, or $(CH_2)_qR^{14}$, wherein q is an integer form 0 to 5, and R^{14} is a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl radical in which at least one hydrogen atom is optionally substituted with a substituent selected from the group consisting of a halogen, OH, OCH_3, NH_2, NO_2, SH, and CN;

W is C(O), C(S), or SO_2; and

R^6 is a cycloalkyl, heterocycloalkyl, aryl, or heteroaryl radical in which at least one hydrogen atom is optionally substituted with a substituent selected from the group

consisting of a halogen, OR^{15}, SR^{15}, $S(O)R^{15}$, SO_2R^{15}, $SO_2NR^{15}R^{16}$, $SO_2N(OH)R^{15}$, CN, $CR^{15}=NR^{16}$, $CR^{15}=N(OR^{16})$, N_3, NO_2, $NR^{15}R^{16}$, $N(OH)R^{15}$, $C(O)R^{15}$, $C(S)R^{15}$, CO_2R^{15}, $C(O)SR^{15}$, $C(O)NR^{15}R^{16}$, $C(S)NR^{15}R^{16}$, $C(O)N(OH)R^{15}$, $C(S)N(OH)R^{15}$, $NR^{15}C(O)R^{16}$, $NR^{15}C(S)R^{16}$, $N(OH)C(O)R^{15}$, $N(OH)C(S)R^{15}$, $NR^{15}CO_2R^{16}$, $N(OH)CO_2R^{15}$, $NR^{15}C(O)SR^{16}$, $NR^{15}C(O)NR^{16}R^{17}$, $NR^{15}C(S)NR^{16}R^{17}$, $N(OH)C(O)NR^{15}R^{16}$, $N(OH)C(S)NR^{15}R^{16}$, $NR^{15}C(O)N(OH)R^{16}$, $NR^{15}C(S)N(OH)R^{16}$, $NR^{15}SO_2R^{16}$, $NHSO_2NR^{15}R^{16}$, $NR^{15}SO_2NHR^{16}$, $P(O)(OR^{15})(OR^{16})$, an alkyl, an alkoxy, an alkylthio, an alkylamino, a cycloalkyl, a cycloalkylalkyl, a heterocycloalkyl, a heterocycloalkylalkyl, an aryl, an aryloxy, an arylamino, an arylthio, an aralkyl, an aryloxyalkyl, an arylaminoalkyl, an aralkoxy, an (aryloxy)alkoxy, an (arylamino)alkoxy, an (arylthio)alkoxy, an aralkylamino, an (aryloxy)alkylamino, an (arylamino)alkylamino, an (arylthio)alkylamino, an aralkylthio, an (aryloxy)alkylthio, an (arylamino)alkylthio, an (arylthio)alkylthio, a heteroaryl, a heteroaryloxy, a heteroarylamino, a heteroarylthio, a heteroaralkyl, a heteroaralkoxy, a heteroaralkylamino, and a heteroaralkylthio,

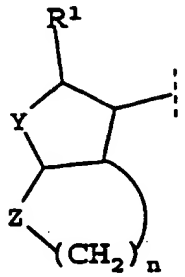
wherein R^{15}, R^{16}, and R^{17} are H, an unsubstituted alkyl, or an unsubstituted alkenyl,

wherein, when at least one hydrogen atom of R^6 is substituted with a substituent other than a halogen, OR^{15}, SR^{15}, CN, N_3, NO_2, $NR^{15}R^{16}$, $C(O)R^{15}$, $C(S)R^{15}$, CO_2R^{15}, $C(O)SR^{15}$, $C(O)NR^{15}R^{16}$, $C(S)NR^{15}R^{16}$, $NR^{15}C(O)R^{16}$, $NR^{15}C(S)R^{16}$, $NR^{15}CO_2R^{16}$, $NR^{15}C(O)SR^{16}$, $NR^{15}C(O)NR^{16}R^{17}$, or $NR^{15}C(S)NR^{16}R^{17}$, at least one hydrogen atom on said substituent is optionally substituted with a halogen, OR^{15}, SR^{15}, CN, N_3, NO_2, $NR^{15}R^{16}$, $C(O)R^{15}$, $C(S)R^{15}$, CO_2R^{15}, $C(O)SR^{15}$, $C(O)NR^{15}R^{16}$, $C(S)NR^{15}R^{16}$, $NR^{15}C(O)R^{15}$, $NR^{15}C(S)R^{16}$, $NR^{15}CO_2R^{16}$, $NR^{15}C(O)SR^{16}$, $NR^{15}C(O)NR^{16}R^{17}$, or $NR^{15}C(S)NR^{16}R^{17}$; or

R^5 and R^6 together comprise a 12 to 18 membered ring comprising at least one additional heteroatom in the ring skeleton which includes the N-W bond of formula (I); and

wherein, said compound inhibits a multidrug-resistant retroviral protease.

2. The compound of claim 1, wherein A is a group of the formula:



3. The method of claim 1 or 2, wherein:

when R^1 is an alkyl, it is a C_1-C_6 alkyl;

when R^1 is an alkenyl it is a C_2-C_6 alkenyl;

when R^1 is a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl, R^1 is a 4-7 membered ring;

when R^7, R^8 or R^9 is an unsubstituted alkyl, it is a C_1-C_6 unsubstituted alkyl;

when R^7, R^8 or R^9 is an unsubstituted alkenyl, it is a C_2-C_6 unsubstituted alkenyl;

R^3 is a 4-7 membered ring;

R^{11} is a 4-7 membered ring;

when R^{12} or R^{13} is an unsubstituted alkyl, it is a C_1-C_6 unsubstituted alkyl;

when R^{12} or R^{13} is an unsubstituted alkenyl, it is a C_2-C_6 unsubstituted alkyl;

when R^{14} is a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl, R^{14} is a 4-7 membered ring;

when R^6 is a cycloalkyl, a heterocycloalkyl, aryl, or a h teroaryl, R^6 is a 4-7 membered ring;

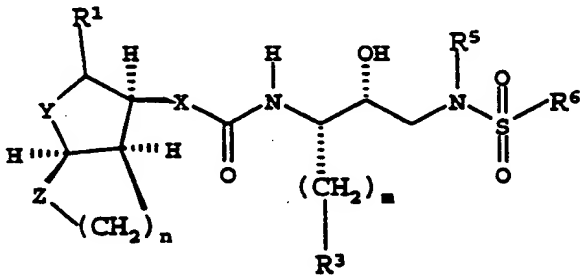
when R^6 is substituted with a substituent that is an alkyl, an alkylthio, or an alkylamino, the substituent comprises from one to six carbon atoms; and

when R^6 is substituted with a substituent that is a cycloalkyl, a heterocycloalkyl, an aryl, or a heteroaryl, the substituent is a 4-7 membered ring;

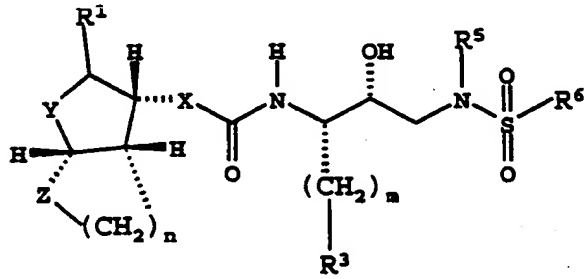
or a pharmaceutically acceptable salt, a prodrug, or an ester thereof.

4. The compound of claim 1 or 2, wherein Q is C(O), R^2 is H, and W is SO_2, or a pharmaceutically acceptable salt, a prodrug, or an ester thereof.

5. The compound of claim 2 represented by the formula:

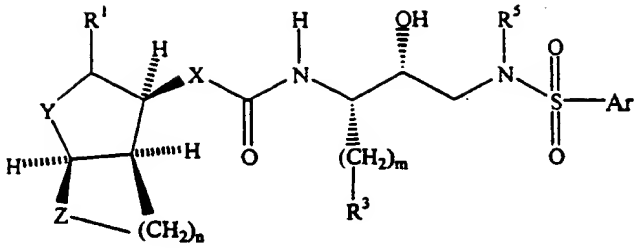


(IA) or

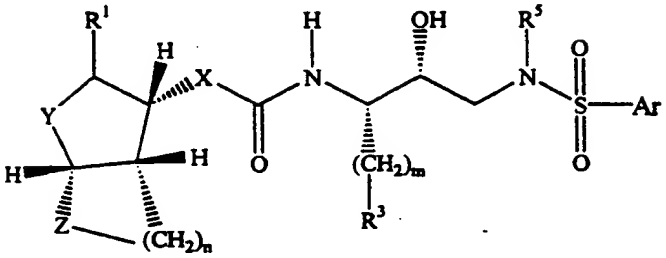


(IB).

6. Th compound of claim 5 represented by the formula:



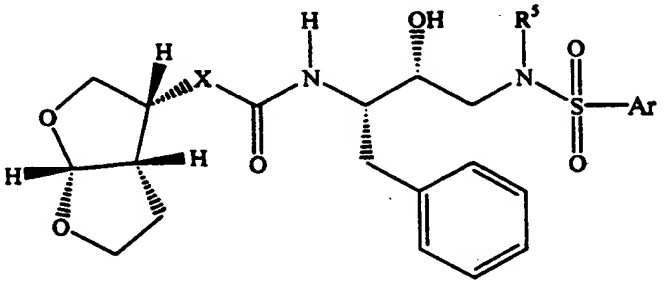
(IC) or



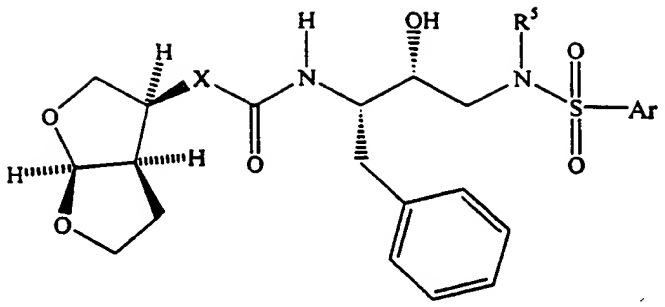
(ID),

wherein Ar is a phenyl which is optionally substituted with a substituent selected from the group consisting of methyl, amino, hydroxy, methoxy, methylthio, hydroxymethyl, aminomethyl, and methoxymethyl.

7. The compound of claim 6 represented by the formula:



(IE) or



(IF).

8. The compound of claim 6 or 7, wherein X is oxygen.

9. The compound of claim 6 or 7, wherein R^5 is isobutyl.

10. The compound of any one of claims 6 or 7, wherein Ar is phenyl substituted at the para-position.

11. The compound of any one of claims 6 or 7, wherein Ar is a phenyl substituted at the meta-position.

12. The compound of claim 6 or 7, wherein Ar is a phenyl substituted at the ortho-position.

13. The compound of any one of claims 6 or 7, wherein Ar is selected from the group consisting of para-aminophenyl, para-toluyl, para-methoxyphenyl, meta-methoxyphenyl, and meta-hydroxymethylphenyl.

14. A pharmaceutical composition which comprises a multidrug-resistant, retroviral protease-inhibiting amount of a compound of any one of claims 1,2, or 5-7 and a pharmaceutically acceptable carrier.

15. The pharmaceutical composition of claim 14, wherein said multidrug-resistant, retroviral protease-inhibiting amount is a multidrug-resistant, HIV protease-inhibiting amount.

16. The pharmaceutical composition of claim 15, wherein multidrug-resistant, HIV protease-inhibiting amount is a multidrug-resistant, HIV-1 protease-inhibiting amount.

17. A method of inhibiting the protease of a multidrug-resistant retrovirus in a mammal infected with a protease-producing, multidrug-resistant retrovirus, which method comprises administering to said mammal a multidrug-resistant, retroviral protease-inhibiting effective amount of a compound of any one of claims 1, 2, or 5-7, so as to inhibit the proliferation of said retrovirus in said mammal.

18. A method of treating a multidrug-resistant retroviral infection in a mammal, which method comprises administering to said mammal a multidrug-resistant, retroviral protease-inhibiting effective amount of a compound of any one of claims 1, 2, or 5-7.

19. The method of claim 17, wherein said multidrug-resistant, retroviral protease-inhibiting amount is a multidrug-resistant, HIV protease-inhibiting amount.

20. The method of claim 18, wherein said multidrug-resistant, retroviral protease-inhibiting amount is a multidrug-resistant, HIV protease-inhibiting amount.

21. The method of claim 19 or 20, wherein said multidrug-resistant, HIV protease-inhibiting amount is a multidrug-resistant, HIV-1 protease-inhibiting amount.

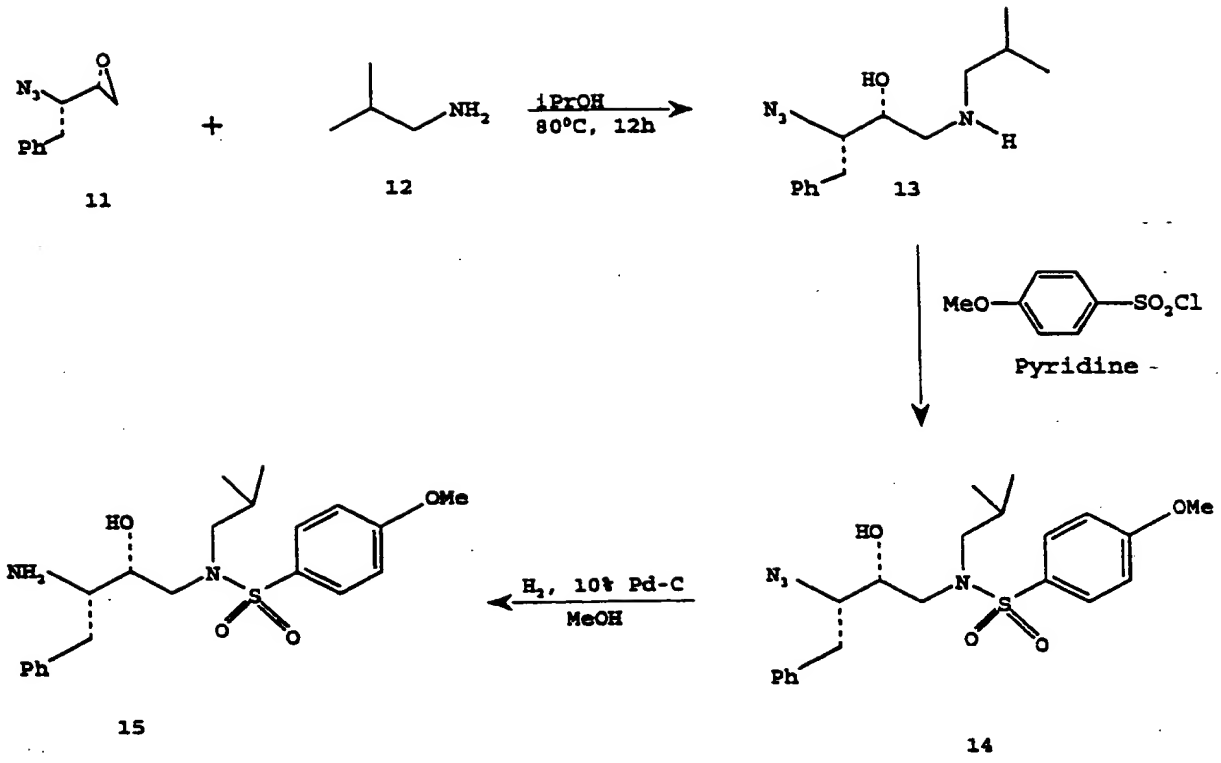

iPrOH
80°C, 12h
MeO
SO2Cl
Pyridine
H2, 10% Pd-C
MeOH
OMe
HO
NH2
N3
Ph
11
12
13
14
15

Fig. 1

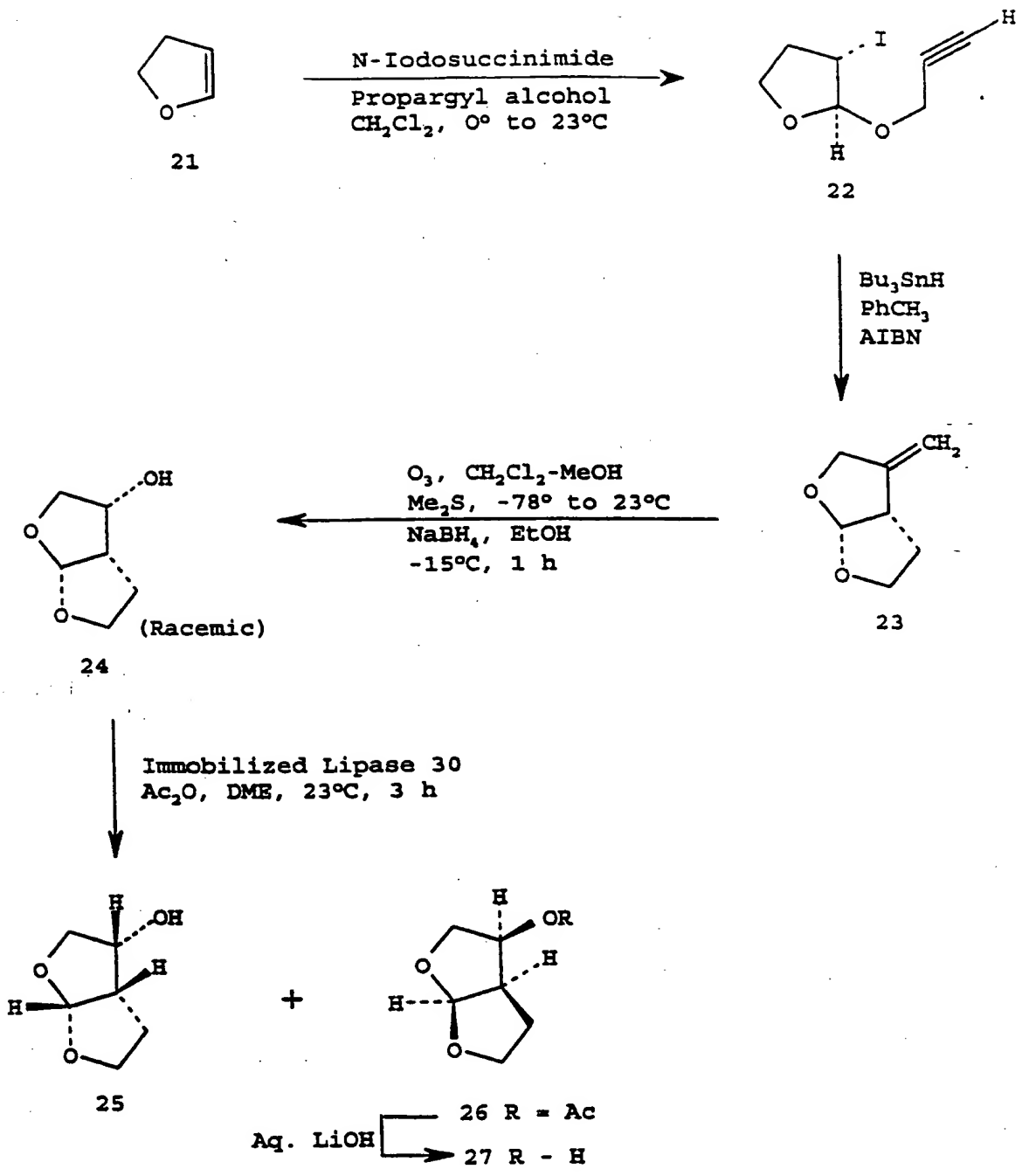
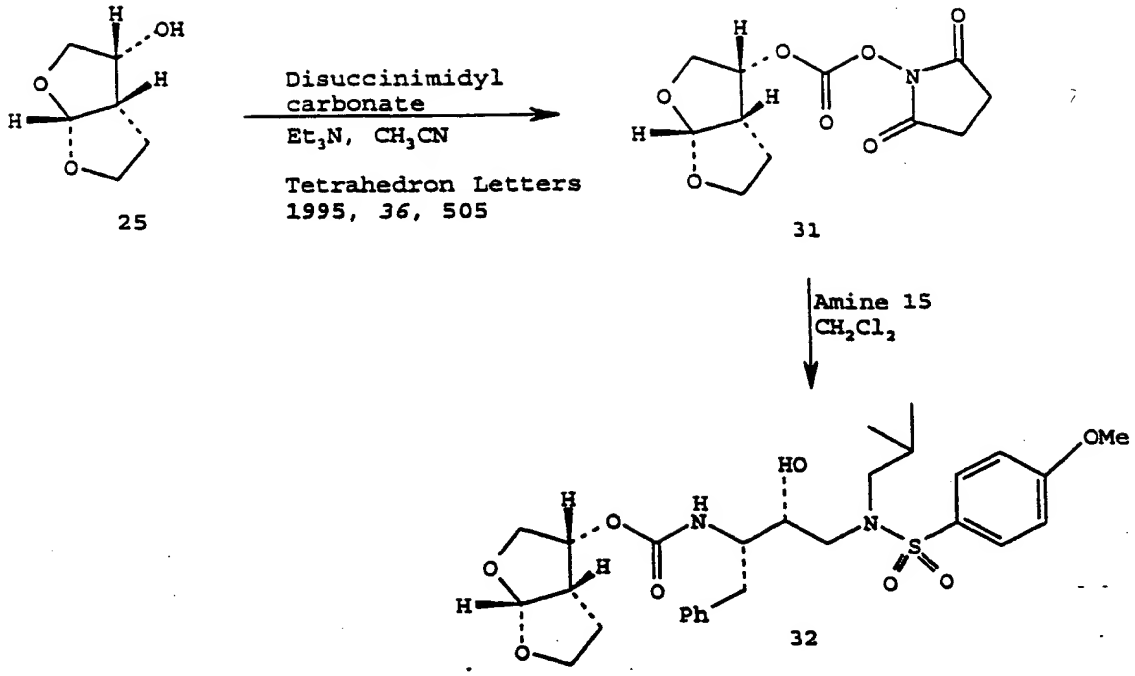
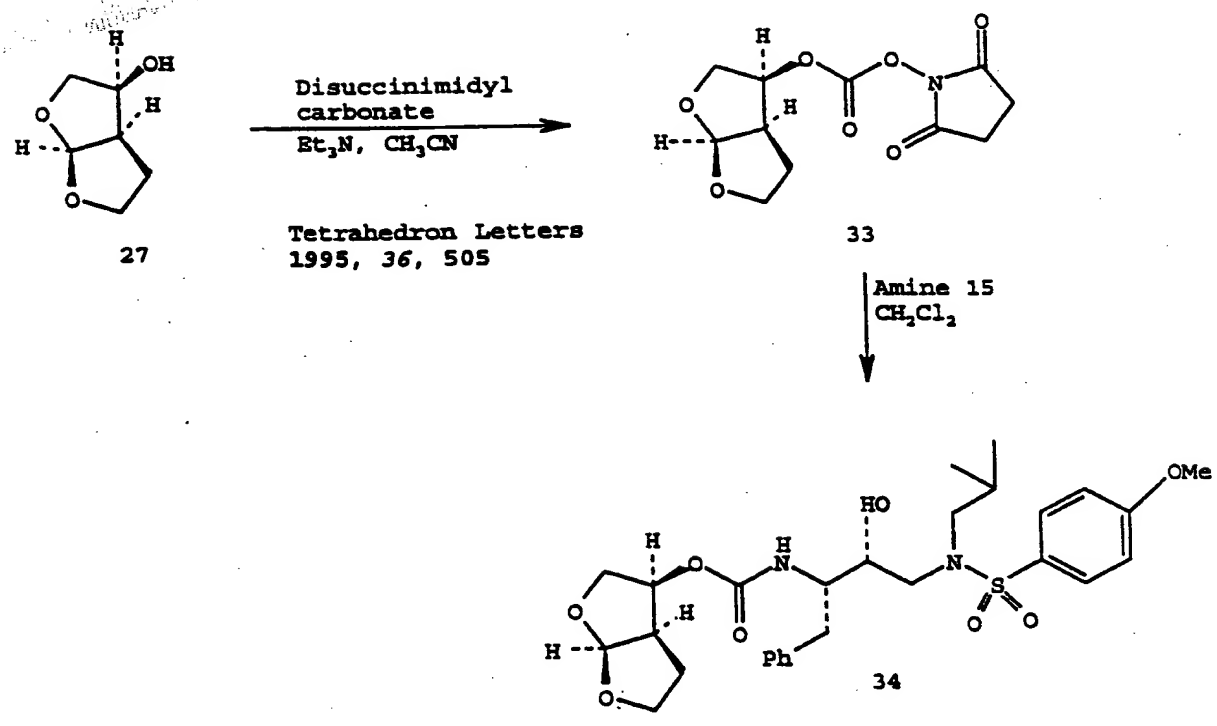

21
N-Iodosuccinimide
Propargyl alcohol
CH_2Cl_2, 0° to 23°C
22
Bu_3SnH
$PhCH_3$
AIBN
23
O_3, CH_2Cl_2-MeOH
Me_2S, -78° to 23°C
$NaBH_4$, EtOH
-15°C, 1 h
(Racemic)
24
Immobilized Lipase 30
Ac_2O, DME, 23°C, 3 h
25
26 R = Ac
Aq. LiOH
27 R - H

Fig. 2



25 31 32

Fig. 3A



27 33 34

Fig. 3B

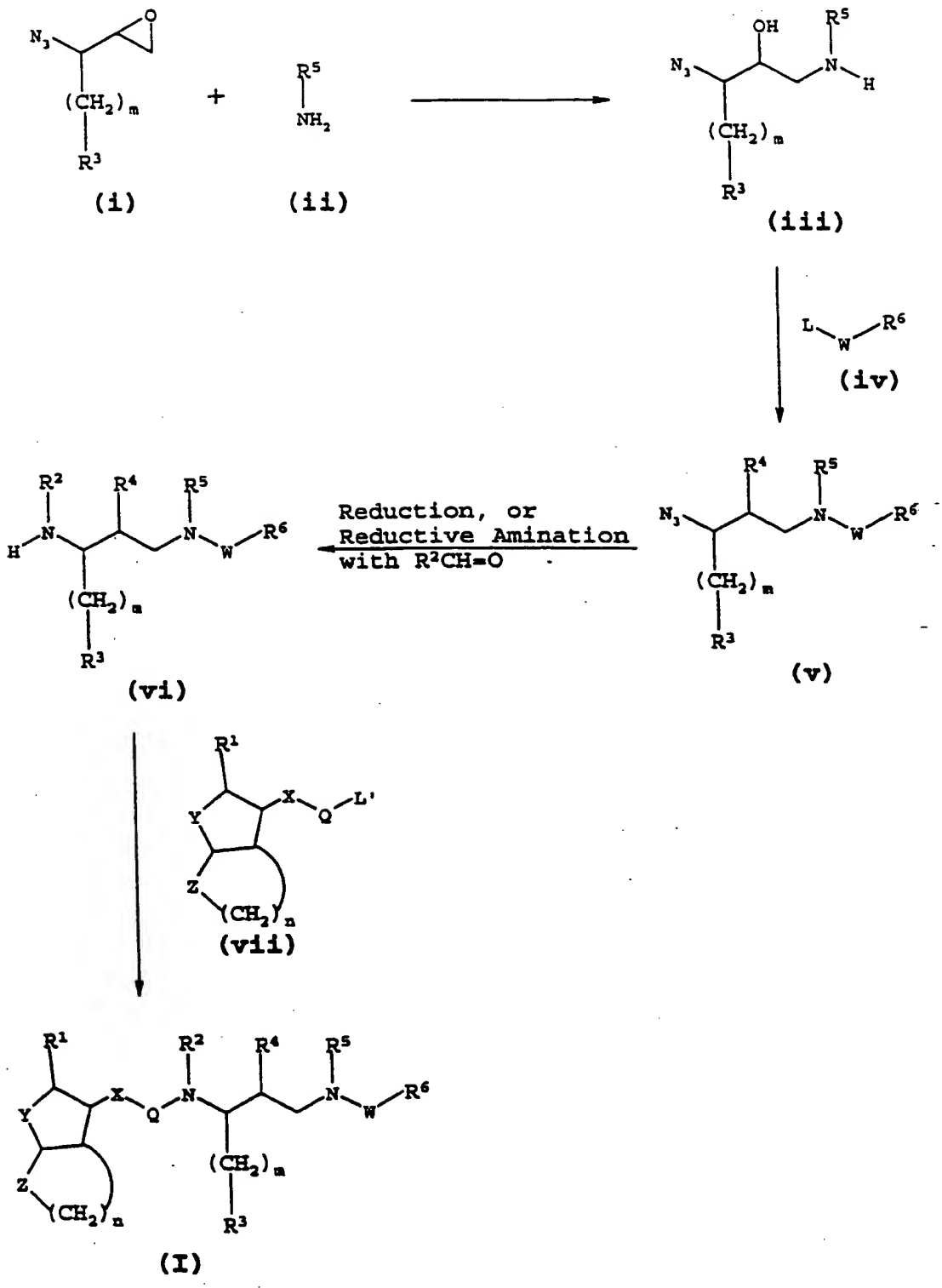
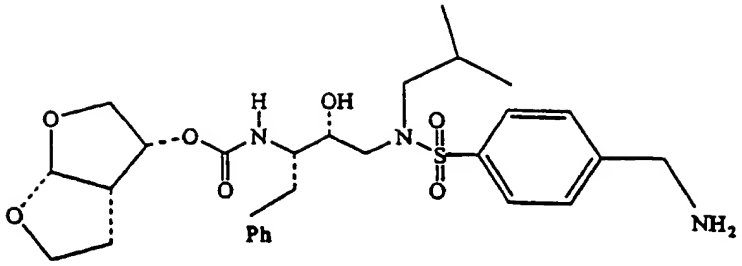
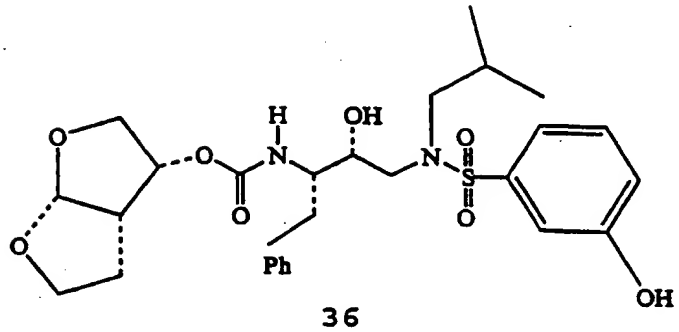

(i)
(ii)
(iii)
(iv)
(v)
(vi)
(vii)
(I)
Reduction, or
Reductive Amination
with R²CH=O

Fig. 4



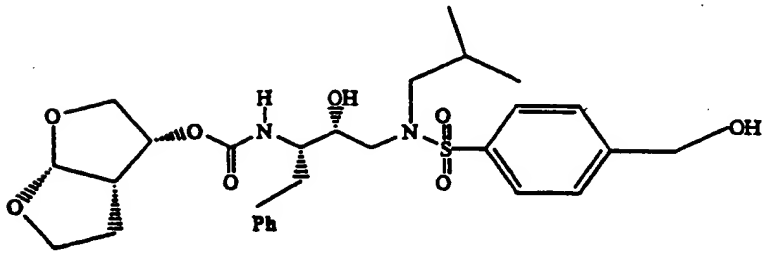
35

Fig. 5A



36

Fig. 5B



37

Fig. 5C

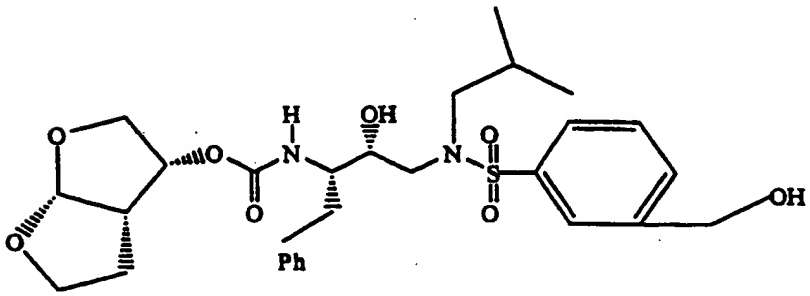


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Fig. 5D